

# Acute allograft rejection in liver transplant recipients: Incidence, risk factors, treatment success, and impact on graft failure

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## Abstract

**Objective:** This study was performed to identify risk factors for acute cellular rejection after liver transplantation (LT).

**Methods:** Consecutive LT recipients who underwent surgery in our institution from 2002 to 2015 were retrospectively evaluated.

**Results:** In total, 176 patients were eligible for statistical analysis. During a mean observation period of  $61.1 \pm 36.3$  months, 43 episodes of acute rejection were evident. Of these, 34 (79.0%) were responsive to methylprednisolone, 3 (7.0%) were treated by adjusting the dosage of immunosuppressive agents, and 6 (14.0%) were methylprednisolone-resistant and treated using anti-thymocyte globulin. Biliary complications (odds ratio [OR] = 4.89, 95% confidence interval [CI] = 2.00–11.98); donor-negative, recipient-positive CMV mismatch (OR = 9.88, 95% CI = 1.18–82.36); sex mismatch (OR = 3.16, 95% CI = 1.31–8.10); and sex mismatch with a female donor (OR = 3.00, 95% CI = 1.10–7.58) were identified as significant risk factors for acute graft rejection after LT.

**Conclusion:** In patients who develop acute cellular rejection after LT, biliary complications should be evaluated as a potential cause. Most acute rejections after LT respond to bolus corticosteroid therapy.

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**Keywords**

Liver transplantation, acute cellular rejection, biliary complications, sex mismatch, cytomegalovirus mismatch, corticosteroids

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**Introduction**

Liver transplantation (LT) is the only curative treatment option currently available for patients with end-stage liver disease.<sup>1</sup> Despite recent advances in immunosuppressive agents, acute allograft rejection remains a common complication of LT, with the incidence ranging from 20% to 40% of liver transplants. In most cases, rejection occurs within the first month following LT.<sup>2,3</sup> Early rejection episodes do not significantly impair long-term graft success or patient outcomes. In contrast, late-onset allograft rejection (>3–6 months following LT) is associated with poor graft survival.<sup>4,5</sup>

Several risk factors for acute allograft rejection have been described, including younger recipient age, HLA-DR mismatch, longer cold ischemic time, and older donor age.<sup>2,6</sup> However, the predictive power of these risk factors differs among studies, and the impact of acute allograft rejection on patient morbidity and mortality following LT is controversial.<sup>6–8</sup>

In the present study, we investigated the risk factors for acute allograft rejection after LT. We also explored the efficacy and success rate of typical treatment options and the impact of an acute rejection on the development of long-term graft failure.

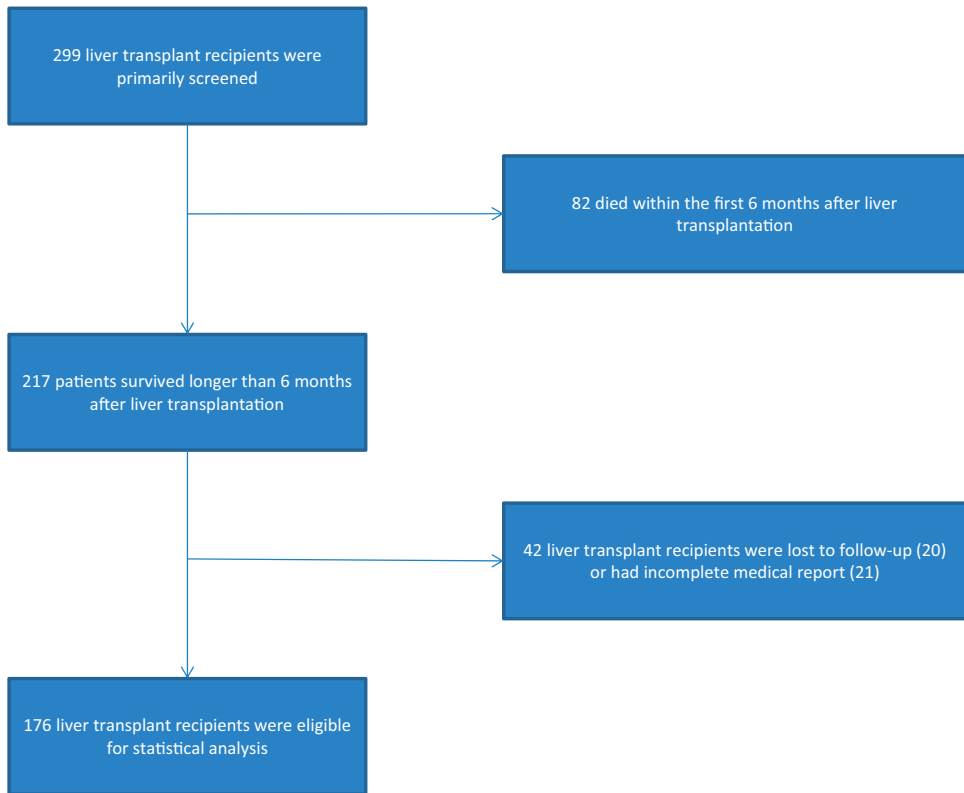
**Patients and methods**

This retrospective study was carried out at the University Hospital Münster. Patients who had undergone LT from 2002 to 2015

and received follow-up at our center were included in this study. The clinical course of each patient was evaluated using electronic patient records. The inclusion criteria were complete post-transplant follow-up of  $\geq 2$  years after LT, age of  $\geq 18$  years, at least one liver biopsy, and the availability of disposable donor data. The flow chart in Figure 1 shows the patient selection in the study. The study was approved by the local ethics committee of the University Hospital of Münster and was performed in accordance with the Declaration of Helsinki. Consent was not required. The present study was a retrospective data analysis of patients who underwent liver transplantation during the last 1.5 decades. Many of these patients had already died when this study was performed. Furthermore, according to German Federal Law, informed consent of patients is not required for retrospective data analyses.

For LT recipients, liver biopsy was performed at 1, 5, and 10 years after LT and in every patient with an unexplained elevation of liver enzymes. In patients with elevated liver enzymes and underlying hepatitis C, B, and/or D virus infection, reinfection was first ruled out using polymerase chain reaction (PCR). Cytomegalovirus (CMV) and Epstein–Barr virus were also excluded as causes of the abnormal liver function using PCR in every unclear case.

Histological examination of biopsy specimens was performed by an expert pathologist. All acute cellular rejections were classified using the Banff Rejection Activity Index (RAI).<sup>9</sup>



**Figure 1.** Flow chart of patient selection in the study.

Long-term graft failure was diagnosed when one or more of the following criteria were met: clinical or histological signs of reappearing cirrhosis, graft failure leading to retransplantation, or allograft-related death. The following clinical variables were assessed for their impact on the occurrence of acute rejection: donor age, donor sex, cold ischemia time, warm ischemia time, donor CMV serostatus, recipient age at the time of LT, recipient sex, sex mismatch, underlying liver disease leading to the initial LT, recipient body mass index, recipient CMV serostatus, CMV mismatch, development of diabetes mellitus before and after LT, occurrence of biliary complications, immunosuppression regimen after LT, Model for End-Stage Liver Disease

score at the time of LT, and total number of transplantations.

The influence of acute rejection on the development of graft failure (as defined above) was subsequently analyzed. For this analysis, we further distinguished between early graft rejection (rejection episodes occurring within 3 months after LT) and late graft rejection (rejection episodes occurring >3 months after LT).

### *Immunosuppressive regimens*

Induction immunosuppression was administered intraoperatively using a single dose of intravenous methylprednisolone (500 mg). For statistical analysis, the administered maintenance immunosuppressive

regimens were subdivided into the following four categories: calcineurin inhibitor (CNI) ± mycophenolate mofetil (MMF), mechanistic target of rapamycin (mTOR) inhibitor ± MMF, CNI ± mTOR inhibitor, and MMF + methylprednisolone.

### *Treatment of acute rejection*

All patients who developed acute cellular rejection were treated using methylprednisolone (500 mg) daily for 3 days. Antithymocyte globulin (ATG) was administered to patients who developed steroid-resistant rejection. Resolution of acute cellular rejection was defined by complete normalization of all liver tests.

### *Biliary complications*

Biliary complications were subdivided into anastomotic strictures and nonanastomotic strictures, biliary leaks, stones, biliary casts, and sludge. The diagnosis of biliary complications was confirmed endoscopically using endoscopic retrograde cholangiography. For predominantly biochemical cholestasis, additional magnetic resonance cholangiopancreatography and/or endoscopic retrograde cholangiography were primarily performed. Acute rejection was first defined after biliary complications were completely resolved. If liver function tests remained abnormal after biliary interventions, the persistence of biliary complications was first evaluated before acute rejection was considered as a cause of the abnormal liver test results. In such cases, a further liver biopsy was performed.

*CMV prophylaxis, treatment, and monitoring.* At our center, all patients except those with a CMV D-/R- status receive antiviral prophylaxis consisting of intravenous ganciclovir at 5 mg/kg/day or valganciclovir at 900 mg once daily for 100 days after LT (these doses are always adjusted to each

patient's renal function). Antiviral prophylaxis is also given if acute rejection is treated with ATG. All LT recipients and every patient with abnormal liver function or symptoms of CMV infection are monitored regularly every 3 months using PCR. In the present study, treatment of CMV began in each patient with CMV-induced organ disease and/or persistent viremia. Asymptomatic patients with low viremia (<1000 copies/mL) were usually observed closely every 2 weeks. In these patients, we first tried to reduce the immunosuppression if this was a reasonable approach. Standard treatment of CMV consisted of ganciclovir at 5 mg/kg twice daily or valganciclovir at 900 mg twice daily. Treatment continued until 2 weeks of negative CMV PCR results were obtained.

### **Statistics**

Statistical analyses were conducted using SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA). Variables with a normal distribution are presented as mean ± standard deviation, whereas non-normally distributed data are presented as median and interquartile range. Prevalence data are reported as absolute frequency and percentage. Univariate logistic regression was initially performed to identify potential risk factors for acute rejection. Variables with significance of  $p < 0.15$  in the univariate analysis were subsequently included in the multivariate analysis. Variables with significance of  $p < 0.05$  in the multivariate analysis were considered statistically significant independent risk factors. The same procedure was performed to evaluate the impact of acute cellular rejection on graft failure. For significant variables, the  $p$ -value, odds ratio (OR), and 95% confidence interval (CI) are reported.

**Table 1.** Clinical and demographic data

LT Donors	
n	176
Age (years)	49.5 ± 15.5
Sex (female, male, unknown)	63 (35.8), 109 (61.9), 4 (2.3)
LT Recipients	
n	176
Age at LT (years)	51.1 ± 11.6
Sex (female, male)	60 (34.1), 116 (65.9)
BMI at LT (kg/m <sup>2</sup> )	25.9 ± 4.9
MELD score at time of LT	21.3 ± 11.5
Biliary complications	46 (26.1)
Cold ischemia time, min	593.8 ± 169.5
Warm ischemia time, min	42.7 ± 11.4
Hepatic artery stenosis or thrombosis	6 (3.4)
Portal vein thrombosis	3 (1.7)
Hepatic venous obstruction	1 (0.6)
Number of LTs	
One	155 (88.1)
Two	19 (10.8)
Three	2 (1.1)
Number of patients with acute rejection	
Total	36 (20.5)
One rejection episode	30 (17.0)
Two rejections episodes	5 (2.8)
Three rejection episodes	1 (0.6)
Pre-transplant diabetes mellitus	41 (23.2)
Post-transplant diabetes mellitus	23 (13.0)
Sex mismatch	
Total	74 (41.8)
Sex mismatch with female donor	39 (22.0)
CMV	
CMV-positive status of recipients	84 (47.5)
CMV-positive status of donors	95 (53.7)
CMV D+/R-	33 (18.6)
CMV D-/R+	22 (12.4)
Underlying disease*	
Hepatitis C	29 (16.5)
Hepatitis B	28 (15.9)
Alcoholic cirrhosis	47 (26.7)
Hepatocellular carcinoma	41 (23.3)
Cholestatic liver disorders	24 (13.6)
Autoimmune hepatitis	12 (6.8)
Acute liver failure	28 (15.4)
Metabolic disorders (Wilson disease, hemochromatosis)	17 (9.7)
Cystic liver disease	8 (4.5)

(continued)

**Table 1.** Continued

Cryptogenic liver cirrhosis	7 (4.0)
Observation time (months)	61.1 ± 36.3
Time between LT and rejection (months), median (range)	2 (0–111)
Protocol biopsy	
Fibrosis	
Stage 0	103 (58.5)
Stage I	38 (21.6)
Stage II	17 (9.6)
Stage III	8 (4.5)
Stage IV	10 (5.7)
Inflammation	
Grade 0	79 (44.9)
Grade I	64 (36.4)
Grade II	25 (14.2)
Grade III	8 (4.6)
Steatosis	
None	98 (55.7)
Mild (<10%)	37 (21.0)
Moderate (10%–30%)	24 (13.6)
Severe (>30%)	17 (9.7)

Data are presented as n (%) or mean ± standard deviation unless otherwise indicated. BMI, body mass index; CMV D+/R–, donor-positive CMV mismatch; CMV D–/R+, recipient-positive CMV mismatch; LT, liver transplantation; MELD, Model of End-stage Liver Disease.

\*Some patients had more than one underlying disease.

## Results

In total, 176 patients met the inclusion criteria and were included in the statistical analysis. Clinical and demographic data of the donors and recipients are presented in Table 1. The mean ages of the donors and recipients were 49.5 ± 15.5 and 51.1 ± 11.6 years, respectively. The numbers of female donors and recipients were 63 (35.8%) and 60 (34.1%), respectively. The mean observation time of this study was 61.1 ± 36.3 months. During this time, 416 biopsies in 176 patients were performed, and 43 histologically verified episodes of acute rejection were observed in 36 (20.5%) LT recipients. Of these LT recipients, 30 (17.0%) developed a single acute rejection, 5 (2.8%)

developed two acute rejections, and 1 (0.6%) developed three acute rejections. Of the 43 acute rejections, 28 (65.1%) occurred within 1 year and 25 (58.1%) occurred within the first 3 months of LT. The mean RAI was 4.2 ± 1.4. The median time between LT and acute rejection was 2 months (range, 0–111 months). Among all rejections, 34 (79.0%) were successfully treated with methylprednisolone, 3 (7.0%) were treated by adjusting the blood levels of immunosuppressive agents, and 6 (14.0%) were methylprednisolone-resistant and treated with ATG. The mean levels of tacrolimus, cyclosporine, and everolimus at the time of diagnosis of the acute rejection were 7.0 ± 3.8, 128 ± 23.3, and 4.6 ± 2.2 ng/mL, respectively. Trough levels

**Table 2.** Dependent and independent risk factors associated with acute graft rejection

Variable	Univariate (p-value)	Multivariate* (p-value)	OR (95% CI)
Biliary complications	0.005	0.001	4.89 (2.00–11.98)
CMV mismatch R+ status	0.082	0.034	9.88 (1.18–82.36)
Sex mismatch	0.069	0.010	3.16 (1.31–8.10)
Sex mismatch with female donor	0.115	0.034	3.0 (1.10–7.58)
Recipient age	0.032	0.065	1.0 (0.96–1.04)
CMV mismatch D+ status	0.274	–	–
Sex mismatch with male donor	0.560	–	–
Donor age	0.530	–	–
Donor sex	0.900	–	–
Cold ischemia time	0.476	–	–
Warm ischemia time	0.875	–	–
Recipient sex	0.597	–	–
Hepatitis C	0.986	–	–
Hepatitis B	0.818	–	–
Autoimmune hepatitis	0.6955	–	–
Hepatocellular carcinoma	0.286	–	–
Cholestatic liver disorders	0.732	–	–
MELD score	0.922	–	–
Number of LTs	0.04	0.296	1.7 (0.62–4.77)
Pre-transplant diabetes mellitus	0.286	–	–
Post-transplant diabetes mellitus	0.408	–	–
Immunosuppression regimen after LT	0.755	–	–

OR, odds ratio; CI, confidence interval; CMV, cytomegalovirus; MELD, Model for End-Stage Liver Disease; LT, liver transplantation.

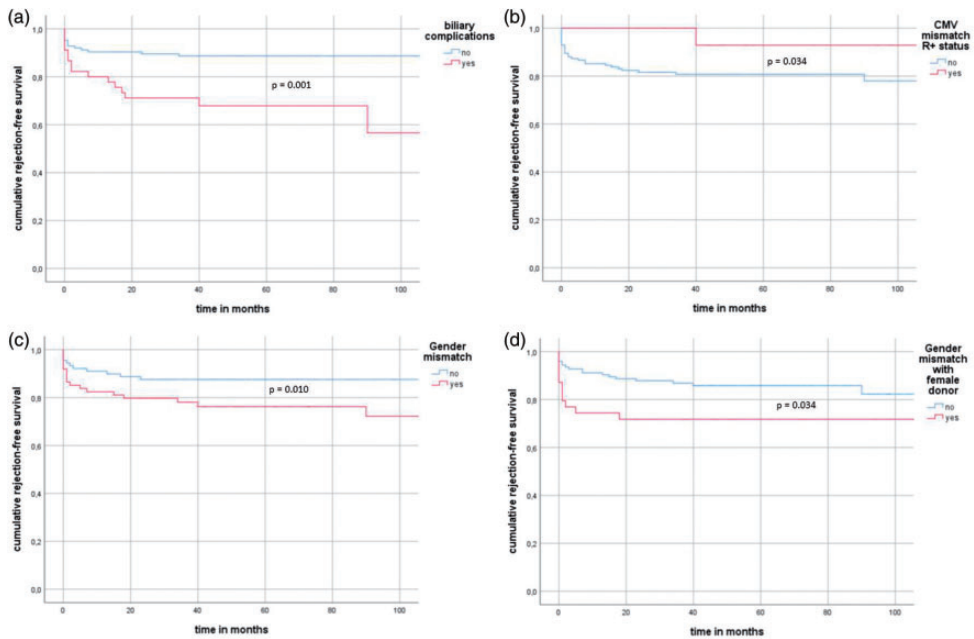
\*Only variables with a significant cutoff of  $p < 0.15$  in the univariate analysis were subsequently included in the multivariate analysis.

were measured in only 5 (11.6%) of the 43 episodes of acute rejection outside the target levels.

A total of 46 (26.1%) patients developed biliary complications after LT. Of these patients, 15 (32%) developed acute cellular rejection. Of these 15 patients, 11 had an anastomotic stricture, 2 had a nonanastomotic stricture, and 2 had biliary leakage. The median time between the diagnosis of biliary complications and the occurrence of acute rejection was 1 month (interquartile range, –1.0 to 11.5) with biliary complications generally occurring before acute rejection. In all cases, the biliary strictures were resolved using repetitive balloon dilation with or without stent insertion. Biliary

leakages were resolved using papillotomy and stent insertion for 6 to 8 weeks.

We performed binary regression analysis to identify risk factors associated with graft rejection (see Materials and Methods). The results of the univariate and multivariate analyses are provided in Table 2. Of the clinical variables assessed, we found that biliary complications after LT ( $p = 0.001$ , OR = 4.89, 95% CI = 2.00–11.98); donor-negative, recipient-positive CMV mismatch ( $p = 0.034$ , OR = 9.88, 95% CI = 1.18–82.36); sex mismatch ( $p = 0.010$ , OR = 3.16, 95% CI = 1.31–8.10); and sex mismatch with a female donor ( $p = 0.034$ , OR = 3.0, 95% CI = 1.10–7.58) were each associated with a greater risk of graft rejection. In contrast,



**Figure 2.** (a–d) Kaplan–Meier survival curves demonstrating acute rejection-free survival in patients based on several risk factors.

acute cellular rejection after LT was not significantly associated with long-term graft failure. Moreover, no difference was observed between early and late rejection, as defined in the Materials and Methods section, with respect to the development of long-term graft failure. The Kaplan–Meier survival curves in Figure 2 show acute rejection-free survival in patients based on several risk factors.

## Discussion

In the early era of LT, acute rejection was a common complication and represented a major cause of long-term graft failure.<sup>4,5</sup> The modern use of immunosuppressive agents, such as CNIs and mTOR inhibitors, has led to significantly reduced rates of acute allograft rejection.<sup>10</sup>

In the present study, acute liver rejection was observed in 20.5% of LT recipients

(Table 1). This incidence is consistent with that of previously reported studies.<sup>2,3</sup> In an earlier study conducted by Wiesner et al.<sup>6</sup> in 1998, a notably higher rejection rate of 65% was reported. In that study, most patients were maintained on an immunosuppression regimen consisting of cyclosporine and prednisolone with or without azathioprine.<sup>6</sup> In contrast, most patients in the current study received a tacrolimus-based immunosuppression generally combined with MMF or an mTOR inhibitor. Several studies have shown that tacrolimus is superior to cyclosporine in preventing acute rejection.<sup>11,12</sup> Furthermore, immunosuppression regimens consisting of tacrolimus with MMF or an mTOR inhibitor have been shown to be highly effective in preventing acute rejection after LT.<sup>13–15</sup> These observations may explain the lower rejection rate in our study compared with the earlier study.<sup>6</sup>



Most acute rejections (65.1%) in our study occurred within 1 year of LT, with a median of 2 months between LT and rejection. This finding is consistent with previous reports.<sup>4</sup> Immune tolerance occurring over time after LT may contribute to this observation.

In our study, 79.0% of recipients who developed acute cellular rejections after LT responded to high-dose bolus methylprednisolone therapy, whereas 14.0% were methylprednisolone-resistant. The remaining 7% of patients were treated by adjusting the blood levels of administered immunosuppressive agents. These results are comparable to those of a previous study conducted by Aydogan et al.,<sup>16</sup> in which 13.7% of acute cellular rejections that occurred after LT were steroid-resistant. All episodes of acute steroid-resistant rejections were resolved successfully using ATG. Our data thus confirm previously published results.<sup>4</sup>

To date, few studies have analyzed the relationship between biliary complications after LT and the occurrence of acute rejection. One systematic review showed that acute rejection was a risk factor for the development of biliary complications.<sup>17</sup> However, whether the converse risk association exists has not been evaluated. In our study, we found that biliary complications after LT were indeed a significant risk factor for the occurrence of acute rejection. In our patient cohort, the risk of an acute rejection following LT was nearly five times higher in patients with than without biliary complications. In these patients, inflammatory triggers caused by biliary complications may have induced the acute rejection. This possibility is consistent with findings suggesting that nonspecific chronic inflammatory triggers may induce an acute rejection after organ transplantation.<sup>18</sup> To our knowledge, the present study is the first to identify biliary complications as a risk

factor for acute rejection in patients undergoing LT.

We also identified donor–recipient sex mismatch as an independent risk factor for acute rejection. In particular, mismatch with a female donor was associated with a higher risk of acute rejection. Several studies have identified sex mismatch with a female donor as a risk factor for allograft failure.<sup>19</sup> However, the underlying mechanisms explaining this association are not well understood. Data indicating a higher risk of acute allograft rejection as a result of sex mismatch are still lacking. A study conducted by Sanada et al.<sup>20</sup> showed a higher rate of acute rejection after pediatric living-donor LT in the case of sex mismatch with a maternal donor.

Several studies have identified CMV infection as a risk factor for acute rejection.<sup>21</sup> However, acute CMV infection of the hepatic allograft may cause symptoms similar to those associated with acute rejection. Serological tests and a liver biopsy should therefore be performed to precisely differentiate between the two scenarios. In the present study, donor-negative, recipient-positive CMV mismatch was associated with a higher risk of acute rejection. Reactivation of CMV infection in LT recipients may trigger the immune system to induce an acute rejection in these patients. This is an important suggestive finding because it is currently recommended that CMV prophylaxis be administered in cases of CMV mismatch with a CMV-positive donor.<sup>22,23</sup> Our data suggest that CMV prophylaxis in cases of donor-negative, recipient-positive CMV mismatch may also prevent acute rejection after LT. However, a prospective study is needed to address this possibility.

Younger recipient age was previously identified as an independent risk factor for acute rejection.<sup>6</sup> In our study, younger recipients were found to be at higher risk in the univariate analysis but not in the

multivariate analysis. The observation that younger recipients were not at higher risk of acute rejection may be explained by the use of highly effective immunosuppression combinations consisting of CNIs and mTOR inhibitors or MMF.

The impact of acute rejection on graft survival after LT remains controversial.<sup>8,24,25</sup> Some studies have suggested that later acute hepatic rejection results in a higher risk of graft failure compared with early acute allograft rejection.<sup>26</sup> However, the definition of late acute graft rejection varies widely among studies, ranging from 3 to 12 months after LT.<sup>4</sup> In the present study, we found no impact of acute rejection on the development of graft failure. Furthermore, there were no significant differences between early- and late-occurring graft rejections and the incidence of allograft failure. A previous study showed that living-donor LT, but not deceased-donor LT, was associated with graft loss due to acute rejection.<sup>27</sup> This observation may partially explain our findings because our treatment center does not perform living-donor LT. Another large-scale study emphasized the declining role of acute rejection on graft loss over several decades in which the first patients who initially received LT were followed up.<sup>24</sup> The findings of this study highlighted how the increasing use of tacrolimus-based immunosuppression has significantly reduced graft failure caused by acute and chronic rejection. The use of modern immunosuppression also explains the mild severity of most acute rejections in the present study (mean RAI,  $4.2 \pm 1.4$ ). This fact may explain the lack of association between acute rejection and the development of graft failure in our study, because most of our patients were maintained on tacrolimus-based immunosuppression.

In the present study, the occurrence of vascular complications was very low and comparable to that found in former studies.<sup>28–30</sup> Hepatic artery thrombosis

and/or stenosis were the most commonly observed vascular complications (3.4% of cases). In general, vascular complications occurred with a very low incidence, making it infeasible to evaluate their role in the development of acute rejection.

The results of our study suggest that in patients receiving LT, biliary complications should always be monitored as a potential trigger of acute rejection. LT recipients with female donor sex mismatch and donor-negative, recipient-positive CMV mismatch are also at higher risk of developing acute rejection and should be observed carefully after LT. The need for CMV prophylaxis after LT in cases of donor-negative, recipient-positive CMV mismatch should also be explored in future prospective studies. Despite controversial data in the literature, successful resolution of acute rejection after LT can avoid graft failure. Most acute rejections after LT respond to bolus corticosteroid therapy. In patients with steroid-resistant rejections, ATG shows excellent therapeutic effectiveness.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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