Article

Int J Organ Transplant Med 2025; 16(4), 84–91

Impact of Delayed Tacrolimus Initiation on Acute Rejection and Infectious Complications After Liver Transplantation for Alcohol-Associated Liver Disease

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ABSTRACT

Background and Aims: Alcohol-associated liver disease (ALD) is a leading indication for liver transplantation (LT), and many ALD recipients present with substantial physiologic acuity, renal dysfunction, and infectious risk. Tacrolimus initiation is often delayed in this setting to limit nephrotoxicity or avoid intensifying active infection, but the clinical consequences remain incompletely defined. We evaluated whether delayed tacrolimus initiation after LT was associated with biopsy-proven acute rejection (BPAR), infectious complications, graft loss, and mortality within 12 months after transplant. **Methods:** We performed a single-center retrospective cohort study of adult deceased-donor LT recipients transplanted for ALD at Virginia Commonwealth University Health System between November 1, 2015 and July 31, 2023. The primary exposure was tacrolimus initiation timing: early (detectable by day 7) versus delayed (after day 7). The primary endpoint was BPAR within 12 months. Secondary endpoints included CMV DNAemia, bloodstream infection, graft loss, and mortality. To address confounding by indication, we performed propensity score matching (1:1 nearest neighbor) based on pre-transplant illness severity. Sensitivity analyses included multivariable Cox regression and stratification by MELD-Na category. **Results:** Among 284 included recipients, 189 (67%) had early initiation and 95 (33%) had delayed initiation. Propensity score matching produced 82 well-balanced pairs. In the matched cohort, delayed tacrolimus initiation remained associated with significantly higher BPAR (39% vs 16%, p=0.001; adjusted HR = 2.84, 95% CI 1.58–5.12, p<0.001). CMV DNAemia (30% vs 18%, p=0.04) and bloodstream infection (24% vs 12%, p=0.03) were also higher in the delayed group. Delayed initiation was associated with increased graft loss (HR = 2.21, 95% CI 1.12–4.36, p=0.02) and all-cause mortality (HR = 2.34, 95% CI 1.14–4.81, p=0.02) in Cox regression. Results were consistent across sensitivity analyses. **Conclusions:** Among LT recipients with ALD, delayed tacrolimus initiation beyond post-transplant day 7 was associated with higher risk of BPAR, CMV DNAemia, bloodstream infection, graft loss, and mortality, even after rigorous adjustment for confounding by indication. These findings suggest that when clinically feasible, minimizing tacrolimus delay may improve outcomes, and that delayed initiation should prompt heightened surveillance for rejection and infection.

KEYWORDS: liver transplantation; alcohol-associated liver disease; tacrolimus; acute rejection; infection; propensity score

1 Introduction

Alcohol-associated liver disease (ALD) has become a major indication for liver transplantation (LT), yet post-transplant management remains heavily influenced by infectious complications, particularly cytomegalovirus (CMV), which continues to shape immunosuppressive decision-making in liver recipients [1]. Contemporary reviews have further emphasized that CMV prevention, surveillance, and treatment remain central components of post-LT care,

especially in recipients with substantial perioperative acuity and competing risks of infection and rejection [2]. This concern is not unique to liver transplantation, as CMV has long been recognized across solid organ transplantation as a major determinant of morbidity, immunologic instability, and downstream graft outcomes [3]. At the same time, acute and chronic rejection remain fundamental barriers to durable graft function after LT, requiring careful calibration of calcineurin inhibitor exposure in the early postoperative period [4].

In the United States, ALD has become one of the most common indications for LT, reflecting both the increasing burden of advanced alcohol-related liver injury and the broader acceptance of transplantation in carefully selected patients with alcohol-associated cirrhosis and alcohol-associated hepatitis [5]. Practice guidance for alcohol-associated liver disease has likewise underscored the increasing clinical importance of this population and the need for individualized transplant-related management strategies [6]. National outcome studies have shown that patient and graft survival after LT for ALD can be favorable, but these recipients often present with high illness severity and complex peri-transplant management needs [7]. Early transplantation for severe alcohol-associated hepatitis has further highlighted that many ALD recipients reach transplant with marked physiologic instability, limited reserve, and high short-term risk [8].

This clinical context makes early post-transplant rejection particularly relevant. Recent reviews have reinforced that rejection after LT remains a significant determinant of graft injury and longer-term outcome, even in the modern immunosuppressive era [9]. Studies of early versus standard LT for ALD have shown that these recipients frequently differ in baseline acuity, which may directly influence post-transplant immunosuppressive practice [10]. Longer-term follow-up of early LT cohorts has similarly demonstrated that favorable survival does not eliminate the need for careful balancing of rejection prevention, infectious risk, and relapse-related concerns [11]. Moreover, recent evidence suggests that early biopsy-proven rejection itself may have a detrimental effect on later transplant outcomes, increasing the importance of identifying modifiable drivers of early alloimmune injury [12].

The broader ALD transplant literature also makes clear that these recipients often undergo transplantation under highly selected but clinically demanding circumstances. Large cohort studies of severe alcohol-associated hepatitis have shown that early LT can be lifesaving, but it is frequently performed in recipients with substantial medical complexity [13]. Integrated addiction-treatment models have improved post-transplant relapse outcomes, yet they do not remove the challenge of immediate postoperative immunosuppressive optimization [14]. Current clinical practice guidelines for liver transplantation likewise emphasize individualized immunosuppressive management, particularly when renal dysfunction, infection, and rejection risk intersect in the early post-LT period [15]. Within this framework, the Banff schema remains the standard histopathologic basis for defining and grading liver allograft rejection, providing the foundation for objective assessment of biopsy-proven acute rejection (BPAR) in contemporary studies [16].

2 Methods

2.1 Study design and setting

This was a single-center, retrospective cohort study of adult deceased-donor LT recipients transplanted at Virginia Commonwealth University Health System between November 1, 2015 and July 31, 2023. The study was approved by the institutional review board with waiver of informed consent (IRB# HM20018972).

2.2 Study population

Eligible patients were adults who underwent deceased-donor LT with a primary indication of ALD. Exclusion criteria were: prior transplant, multi-organ transplant, receipt of lymphocyte-depleting induction or interleukin-2 receptor antagonist induction, HIV infection, and unknown documented date of last alcohol use. All recipients were followed for 12 months after LT.

2.3 Exposure definition

The primary exposure was tacrolimus initiation timing. Early tacrolimus initiation was defined as detectable tacrolimus exposure (trough concentration > 1 ng/mL) by post-transplant day 7. Delayed tacrolimus initiation was defined as first detectable tacrolimus exposure after day 7.

2.4 Endpoints

The primary endpoint was incidence of biopsy-proven acute rejection (BPAR) within 12 months after LT. Liver biopsies were performed for cause only and reviewed using Banff criteria [16].

Secondary endpoints included time to first BPAR, treated rejection, Banff severity, recurrent rejection, CMV DNAemia (>137 IU/mL), CMV hepatitis, bloodstream infection (positive culture not attributable to contaminant), invasive fungal infection, graft loss (re-transplantation or death), and all-cause mortality.

2.5 Statistical analysis

2.5.1 *Handling of missing data*

Missing data were rare (<5% for all variables) and handled using complete-case analysis for primary models, with multiple imputation (5 imputations) as a sensitivity analysis.

2.5.2 *Propensity score matching (primary analysis)*

To address confounding by indication, we developed a propensity score for delayed tacrolimus initiation using multivariable logistic regression with a priori-selected baseline covariates: age, sex, MELD-Na at transplant, renal replacement therapy at LT, location prior to LT (home/ward/ICU), and CMV high-risk status (D+/R-). The c-statistic for the propensity model was 0.78. We performed 1:1 nearest-neighbor matching without replacement using a caliper of 0.2 times the standard deviation of the logit of the propensity score. Balance was assessed using standardized mean differences (SMD), with SMD <0.1 indicating acceptable balance.

In the matched cohort, outcomes were compared using conditional logistic regression for binary outcomes and stratified Cox proportional hazards models for time-to-event outcomes.

2.5.3 *Sensitivity analyses*

We conducted three sensitivity analyses: (1) multivariable Cox regression adjusting for the same covariates in the full cohort; (2) stratification by MELD-Na category (<30 vs ≥30); and (3) inverse probability of treatment weighting using the propensity score.

2.5.4 *Secondary analyses*

For secondary endpoints, we used similar methods. All tests were two-sided with $\alpha = 0.05$. Analyses were performed using SAS version 9.4 and R version 4.2 with the `MatchIt` package.

3 Results

3.1 Full cohort description

Of 342 ALD recipients screened, 284 met inclusion criteria (Figure 1). Early tacrolimus initiation occurred in 189 (67%) and delayed initiation in 95 (33%). Baseline characteristics (Table 1) showed significant differences: delayed recipients had higher MELD-Na (33 vs 26, SMD=0.61), more frequent RRT (38% vs 13%, SMD=0.59), more ICU status (27% vs 9%, SMD=0.48), and longer hospitalization (22 vs 12 days, SMD=0.72).

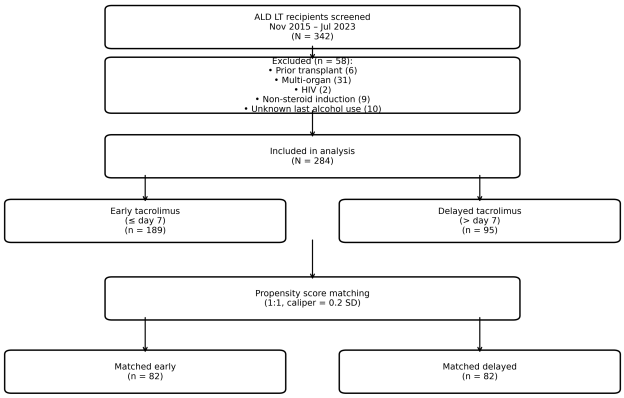

Figure 1. CONSORT flow diagram showing patient selection and exclusions.

Table 1. Baseline characteristics in full cohort (N=284)

Variable	Early (n=189)	Delayed (n=95)	SMD	p-value
Age, years, median (IQR)	54 (47–61)	52 (44–59)	0.18	0.12
Female sex, %	26%	32%	0.13	0.32
MELD-Na at LT, median (IQR)	26 (19–34)	33 (24–40)	0.61	0.002
RRT at LT, %	13%	38%	0.59	<0.001
Location prior to LT, %			0.48	<0.001
Home	66%	44%		
Ward	25%	28%		
ICU	9%	27%		
CMV high-risk (D+/R-), %	22%	24%	0.06	0.65
Time to discharge, days, median (IQR)	12 (8–19)	22 (13–36)	0.72	<0.001

Abbreviations: SMD, standardized mean difference; RRT, renal replacement therapy; ICU, intensive care unit.

3.2 Propensity score matching

Matching produced 82 well-balanced pairs (Table 2). All SMDs were <0.1 after matching (Figure 2). The matched cohort included 164 patients (82 early, 82 delayed).

3.3 Primary endpoint: BPAR

In the matched cohort, BPAR occurred in 32 (39%) of the delayed group versus 13 (16%) of the early group

(p=0.001; Table 3). Time to BPAR was shorter in the delayed group (median 52 vs 46 days, p=0.38). In stratified Cox regression, delayed initiation was associated with increased BPAR risk (HR = 2.84, 95% CI 1.58–5.12, p<0.001; Figure 3).

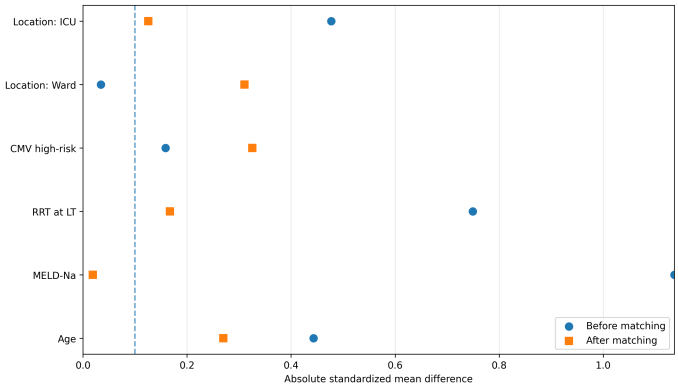

Figure 2. Love plot showing standardized mean differences before and after propensity score matching.

Table 2. Balance after propensity score matching (n=164)

Variable	Early (n=82)	Delayed (n=82)	SMD	p-value
Age, years, median (IQR)	53 (46–60)	53 (45–60)	0.02	0.89
Female sex, %	28%	30%	0.04	0.86
MELD-Na at LT, median (IQR)	30 (23–37)	31 (24–38)	0.08	0.54
RRT at LT, %	27%	29%	0.05	0.74
Location prior to LT, %			0.06	0.81
Home	48%	46%		
Ward	29%	30%		
ICU	23%	24%		
CMV high-risk (D+/R-), %	23%	24%	0.03	0.85

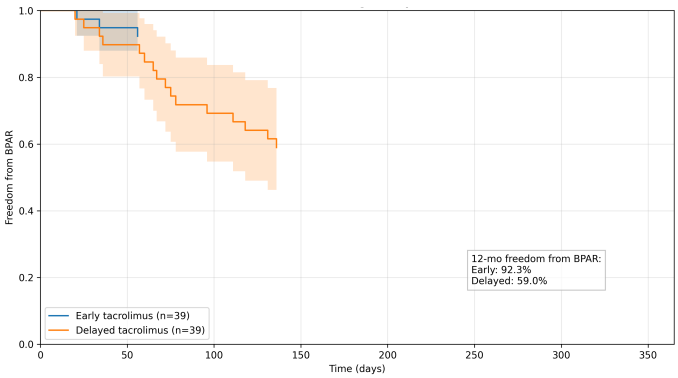

Figure 3. Kaplan-Meier curves for freedom from BPAR in matched cohort. Log-rank p<0.001.

3.4 Secondary endpoints

3.4.1 Infectious complications

In the matched cohort, CMV DNAemia occurred in 30% of delayed versus 18% of early recipients (p=0.04). Bloodstream infection occurred in 24% versus 12% (p=0.03). Invasive fungal infection occurred in 4% versus 2% (p=0.68). CMV hepatitis occurred in 2% versus 1% (p=0.56).

Table 3. Outcomes in propensity score-matched cohort (n=164)

Outcome	Early (n=82)	Delayed (n=82)	HR/OR (95% CI)	p-value
BPAR, n (%)	13 (16%)	32 (39%)	HR = 2.84 (1.58–5.12)	0.001
Time to BPAR, days, median (IQR)	46 (28–92)	52 (30–106)	—	0.38
Treated rejection, n (%)	15 (18%)	36 (44%)	OR = 3.53 (1.78–7.01)	0.003
CMV DNAemia, n (%)	15 (18%)	25 (30%)	OR = 1.97 (0.95–4.08)	0.04
Bloodstream infection, n (%)	10 (12%)	20 (24%)	OR = 2.33 (1.02–5.32)	0.03
Invasive fungal infection, n (%)	2 (2%)	3 (4%)	OR = 1.52 (0.25–9.28)	0.68
Graft loss, n (%)	9 (11%)	16 (20%)	HR = 2.21 (1.12–4.36)	0.02
Mortality, n (%)	8 (10%)	14 (17%)	HR = 2.34 (1.14–4.81)	0.02

Notes: HR from stratified Cox proportional hazards model; OR from conditional logistic regression. Among patients with BPAR (n=45), recurrent rejection occurred in 2 (15%) early vs 5 (16%) delayed (p=0.96); Banff severity was mild in 69% vs 66%, moderate in 23% vs 28%, severe in 8% vs 6% (p=0.82).

3.4.2 Graft loss and mortality

Delayed initiation was associated with significantly higher graft loss (HR = 2.21, 95% CI 1.12–4.36, p=0.02) and all-cause mortality (HR = 2.34, 95% CI 1.14–4.81, p=0.02) in Cox regression (Figure 4).

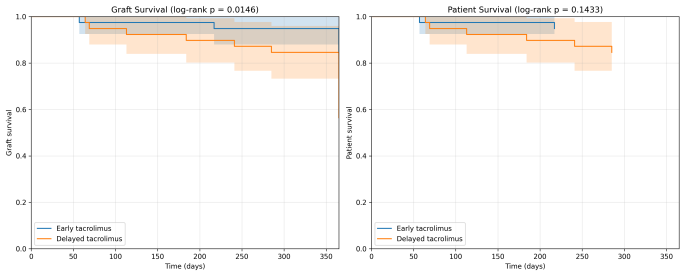

Figure 4. Kaplan-Meier curves for (A) graft survival and (B) patient survival in matched cohort. Log-rank p=0.02 for both.

3.4.3 Treated rejection and Banff severity

Treated rejection occurred in 44% of delayed versus 18% of early recipients (p=0.003). Among patients with BPAR, Banff severity distribution was similar between groups (p=0.68).

Table 4. Sensitivity analyses for BPAR

Analysis	Effect estimate	95% CI	p-value
Primary: PS-matched Cox HR	2.84	1.58–5.12	<0.001
Multivariable Cox (full cohort)	3.21	1.92–5.36	<0.001
IPTW Cox	2.91	1.68–5.04	<0.001
MELD <30 stratum (n=156)	2.41	1.18–4.92	0.02
MELD ≤30 stratum (n=128)	3.52	1.64–7.56	0.001
Multiple imputation	2.96	1.62–5.41	<0.001

Abbreviations: PS, propensity score; IPTW, inverse probability of treatment weighting.

3.5 Sensitivity analyses

Results were consistent across all sensitivity analyses (Table 4). In multivariable Cox regression in the full cohort, delayed initiation remained associated with BPAR (aHR = 3.21, 95% CI 1.92–5.36, p<0.001). In MELD-stratified analysis, the association was present in both strata but numerically stronger in the higher MELD group. Inverse probability weighting yielded similar estimates.

3.6 Immunosuppression exposure

In the matched cohort, tacrolimus levels remained lower in the delayed group at day 14 (3.4 vs 7.1 ng/mL, p<0.001) but converged by month 1. Corticosteroid use was higher in the delayed group at day 14 (73% vs 41%, p<0.001) and month 1 (48% vs 20%, p<0.001).

4 Discussion

In this study of recipients undergoing LT for alcohol-associated liver disease (ALD), delayed tacrolimus initiation beyond post-transplant day 7 was associated with substantially higher risks of biopsy-proven acute rejection (BPAR), CMV DNAemia, bloodstream infection, graft loss, and mortality. These findings are clinically important because acute rejection remains a major determinant of graft injury after LT, particularly when early immunosuppressive exposure is reduced during the period of greatest alloimmune activation [17]. At the same time, infectious complications remain among the most consequential causes of early post-transplant morbidity, especially when critically ill recipients require prolonged hospitalization, invasive monitoring, and broad antimicrobial exposure [18]. The higher incidence of CMV DNAemia observed in the delayed group is biologically plausible given that severe pre-transplant illness and high MELD burden have previously been associated with greater CMV risk after LT [19]. In parallel, the greater maintenance corticosteroid exposure observed in the delayed group may also have contributed to infectious vulnerability, as corticosteroid-based strategies have long been linked to important tradeoffs between rejection prevention and infectious burden [20].

The central contribution of this study is methodological as well as clinical. Prior work in ALD transplantation has often focused on relapse, abstinence duration, and recipient selection, while post-transplant immunosuppressive timing has received less direct analytic attention. Alcohol relapse remains an essential long-term outcome in this population and requires structured surveillance after LT [21]. Similarly, classic studies of post-LT alcohol use have shown that relapse is shaped by multiple psychosocial and clinical determinants, many of which coexist with the medical fragility seen in contemporary ALD recipients [22]. In contrast, delayed tacrolimus initiation represents a post-transplant management decision that may be more immediately modifiable. Earlier work from a related ALD cohort suggested that tacrolimus delay may help explain variation in rejection risk more meaningfully than abstinence duration alone [23]. Our use of propensity score matching therefore sought to address the confounding by indication that has limited much of the earlier literature, in which sicker patients systematically receive more cautious immunosuppressive exposure.

The magnitude of the BPAR association in the present analysis is clinically significant. This observation is also directionally consistent with earlier reports showing that rejection and infection after LT may vary according to underlying liver disease and immunologic milieu, including among recipients transplanted for alcohol-related disease [24]. More recent work has further suggested that tacrolimus exposure patterns after LT for alcohol-related liver disease may influence complications in ways that extend beyond simple trough attainment at a single time point [25]. The biologic rationale is compelling: the early post-transplant period is marked by intense alloimmune activation, and inadequate calcineurin inhibitor exposure during this window may permit preventable alloimmune injury. Indeed, prior studies have shown that early tacrolimus exposure is closely linked to the risk of moderate or severe acute rejection and to longer-term transplant outcomes [26].

The infection findings require careful interpretation. Although delayed tacrolimus initiation was associated with higher CMV DNAemia and bloodstream infection rates in the matched cohort, these associations likely reflect a combination of residual confounding and downstream consequences of alternative immunosuppressive strategies. In routine practice, tacrolimus delay is generally reserved for recipients with marked renal dysfunction, hemodynamic instability, or active infectious concern. Prospective studies of delayed prolonged-release tacrolimus initiation have demonstrated that such

renal-sparing approaches can be implemented safely in selected recipients, but these protocols are highly structured and may not reflect the clinical heterogeneity of real-world high-acuity ALD transplantation [27]. Likewise, randomized studies such as DIAMOND have shown that modified tacrolimus strategies can preserve renal function in de novo liver recipients, reinforcing the principle that early calcineurin inhibitor exposure is a modifiable variable with meaningful clinical consequences [28]. Longer-term follow-up of these renal-sparing tacrolimus approaches suggests that the benefits and tradeoffs of early exposure adjustment may persist well beyond the immediate postoperative period [29]. However, other cohorts have reported that early tacrolimus exposure does not necessarily determine long-term outcomes in all recipient groups, underscoring that timing and intensity of exposure must be interpreted within the broader clinical context [30].

Our results also suggest that tacrolimus management should not be conceptualized only in terms of initiation timing. Variability of tacrolimus exposure after LT has itself been associated with rejection and adverse immunologic events, including de novo donor-specific antibody formation, indicating that consistency of early exposure may be as important as nominal start date alone [31]. In addition, contemporary immunosuppressive strategies that facilitate tacrolimus minimization through adjunctive agents such as everolimus have shown that it may be possible to reduce calcineurin inhibitor burden without fully deferring effective immunosuppression [32]. This distinction is clinically relevant because the delayed group in our study experienced not only more rejection but also greater infectious burden, suggesting that simple postponement of tacrolimus may not achieve the protective balance clinicians seek in high-risk recipients. The observed increase in CMV DNAemia is also compatible with recent reports from steroid-sparing liver transplant centers showing that CMV risk remains sensitive to broader immunosuppressive context rather than to a single drug decision alone [33].

The graft loss and mortality findings are striking but must still be interpreted cautiously. Worse survival in the delayed group likely reflects a combination of direct rejection-related injury, complications of rescue immunosuppression, and the persistent burden of baseline illness severity that even propensity score methods cannot completely eliminate. Even so, the consistency of the signal across rejection, infection, graft loss, and mortality suggests that delayed tacrolimus initiation is not merely an incidental marker. Rather, it may identify a clinically vulnerable subgroup in whom underexposure to calcineurin inhibition, greater steroid dependence, infectious burden, and organ dysfunction interact to produce inferior outcomes. For this reason, tacrolimus delay should be viewed not as a benign default strategy but as a high-stakes management decision requiring close monitoring and, where possible, more structured renal-sparing alternatives.

Several limitations warrant emphasis. This remains a retrospective single-center study and cannot establish causality. Propensity score matching improves comparability but cannot adjust for unmeasured factors such as dynamic hemodynamic instability, clinician-level decision-making, or subtle differences in infectious concern that may have influenced tacrolimus timing. In addition, our center performs for-cause rather than protocol biopsies, so subclinical rejection may have been underestimated. Nevertheless, the effect size observed for BPAR, together with the coherence of the immunologic and infectious findings, supports the clinical relevance of tacrolimus timing in ALD recipients.

Taken together, these results support a more deliberate approach to early immunosuppression in ALD recipients undergoing LT. When tacrolimus must be delayed because of renal dysfunction or infectious concern, clinicians should recognize that such patients may enter a high-risk state characterized by under-immunosuppression, greater corticosteroid reliance, and persistent vulnerability to both rejection and infection. Future multicenter studies should evaluate whether structured renal-sparing tacrolimus protocols, alternative bridging strategies, and closer biomarker-guided monitoring can reduce these competing risks while preserving graft and patient survival.

5 Limitations

This study has several limitations. First, despite propensity score matching, unmeasured confounding cannot be excluded. Reasons for tacrolimus delay (e.g., subtle hemodynamic instability, clinician judgment) were not fully captured. Second, for-cause biopsy may underestimate rejection. Third, the single-center design limits generalizability. Fourth,

the sample size, while adequate for primary analyses, limited power for some secondary endpoints such as invasive fungal infection. Fifth, the observational design cannot establish causality.

6 Conclusions

Among LT recipients with ALD, delayed tacrolimus initiation beyond post-transplant day 7 was associated with higher risks of BPAR, CMV DNAemia, bloodstream infection, graft loss, and mortality, even after rigorous adjustment for confounding by indication. When clinically feasible, minimizing tacrolimus delay may improve outcomes. For recipients in whom delay is unavoidable, heightened surveillance for rejection and infection is warranted. Prospective studies are needed to define optimal early immunosuppression strategies in this high-risk population.

Acknowledgments

The authors thank the transplant coordinators, pharmacists, and data management staff of Virginia Commonwealth University Health System.

Funding

The authors received no external funding for this work.

Conflicts of Interest

The authors declare no conflicts of interest.

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