Clinical Transplantation

WILEY

Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

ORIGINAL ARTICLE OPEN ACCESS

Long-Term Outcomes Among Lung Transplant Recipients With High-Risk Cytomegalovirus Mismatch Managed With a Multimodality Regimen

Natasha Banga | Rohan Kanade | Anishka Kappalayil | Irina Timofte | Adrian Lawrence | Srinivas Bollineni | Vaidehi Kaza | Fernando Torres

Lung Transplant Program, UT Southwestern Medical Center, Dallas, Texas, USA

Correspondence: Fernando Torres (Fernando.torres@utsouthwestern.edu)

Received: 24 March 2025 | **Revised:** 12 May 2025 | **Accepted:** 11 June 2025

Funding: Fernando Torres received consulting fees from Kamada Inc. No other disclosures.

Keywords: CMV resistance | CMV viremia | donor-derived | post-transplant infections

ABSTRACT

Background: Lung transplant (LT) recipients with high-risk cytomegalovirus (CMV) mismatch donors (donor seropositive, recipient seronegative) have worse early and late outcomes. We sought to describe the outcomes among high-risk mismatch patients managed using proactive monitoring and multimodality prophylaxis and management protocol.

Methods: We included patients with single or bilateral lung transplants between January 2012 and December 2016 ($n = 324$). The patients were classified into two groups: high-risk CMV mismatch (R−/D+): $n = 83$ (25.6%) and non-high-risk CMV mismatch ($n = 241$). Post-LT follow-up period ranged from 8 to 12 years. Post-transplant survival was analyzed as the primary outcome variable.

Results: There was no difference in LT recipients' baseline and post-transplant characteristics with and without CMV-mismatch donors. The mismatch group experienced a significantly higher frequency and burden of CMV viremia ($p < 0.001$) and resistant viremia ($p < 0.001$). Regardless, the two groups had similar long-term outcomes with no statistically significant difference in CLAD-free survival at 3 years or overall post-transplant survival. On Cox proportional hazard analysis, transplant indication was the only independent predictor of post-transplant survival ($p = 0.004$).

Conclusions: A proactive multimodality CMV management protocol consisting of antiviral agents (ganciclovir/valganciclovir) and immune augmentation with CMV immune globulin may improve outcomes among high-risk CMV mismatch LT recipients.

1 | Introduction

Cytomegalovirus (CMV) is the most common donor-derived infection among patients undergoing lung transplantation (LT) [1]. CMV infection is a significant contributor to morbidity and mortality among LT patients [2]. The impact of CMV infection among transplant recipients encompasses both direct and indirect effects. Apart from allograft injury from CMV pneumonitis, CMV increases the risk of co-infection with other organisms [3, 4]. In addition, CMV activates alloimmune pathways, leading to an increased risk of acute rejection [5] as well as chronic lung allograft dysfunction (CLAD) [6].

Abbreviations: AKI, acute kidney injury; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CPB, cardiopulmonary bypass; PGD, primary graft dysfunction; VTE, venous thromboembolism.

The risk of CMV infection and its related complications varies based on the donor and recipient CMV serological matching status. Specifically, seronegative recipients who receive organs from seropositive donors are at the highest risk of CMV infection-related complications [7] and are often referred to as high-risk CMV mismatch recipients. Recognition of the significant risks of CMV infection has prompted widespread practice of prophylactic antivirals with or without augmentation of passive immunity among these patients [4]. Indeed, this practice appeared to be associated with improved outcomes among high-risk mismatch patients, with post-transplant survival being similar to that of other recipients [8]. However, these findings have not been replicated in subsequent studies where more recent registry studies based on the analysis of data from across the United States [2, 9], as well as single-center studies [10–12], have found high-risk CMV mismatch to be associated with worse post-transplant survival. Perhaps this is driven by the significant variability in the practice patterns among transplant programs where the use of regimen for CMV prophylaxis, including the medication, its dose, and duration of therapy, is highly variable [9].

Given the significant risk of CMV infection and adverse outcomes among high-risk CMV-mismatch patients, our program developed a protocolized approach consisting of a multimodality pharmacotherapeutic strategy for all recipients with high-risk CMV-mismatch transplants. The current study sought to report our experience using this protocol over a 5-year period. We describe various early and late morbidity and mortality endpoints among patients based on their high-risk CMV mismatch.

2 | Methods

This was a single-center retrospective case-control study conducted at the University of Texas Southwestern Medical Center in Dallas, Texas. The institutional review board granted approval for the study with a waiver of patient consent (IRB# STU-2024-0671).

2.1 | Study Group

The institutional lung transplant database was reviewed. We included all patients who underwent single or bilateral LT between January 2012 and December 2016 (final $n = 324$; mean age 56.3 ± 13.3 years, males 61.1%). All patients had completed at least 8 years of post-transplant follow-up.

2.2 | Patient Management

The serostatus of the donors or recipients was not considered during donor selection. As part of the routine management, each recipient and their respective donor had their CMV serostatus documented upon arrival from the operating room. Seronegative recipients who were transplanted from seropositive donors were designated as high-risk CMV mismatches. The CMV mismatch status did not affect the decision regarding the use, type, and dose of the induction agent or subsequent immunosuppression regimen. The patient's immunosuppressive (IS) regimen was similar for all patients. Basiliximab induction was used among older patients (>65 years) and those needing cardiopulmonary bypass. The IS regimen consisted of oral prednisone (started at 1 mg/kg in divided doses, slow taper to a baseline of 15 mg at the end of 3 months and 7.5 mg by the end of the 1st year), calcineurin inhibitor (tacrolimus being the preferred agent with target trough levels between 10 and 15 ng/mL), and cell cycle inhibitor (azathioprine being the preferred agent with mycophenolate as the alternative). Post-transplant monitoring, including outpatient follow-up visits, lab work, infection screening, surveillance bronchoscopies, and imaging, was also similar for all patients.

2.3 | CMV Protocol

All patients received lifelong CMV prophylaxis in a protocolized manner based on the CMV matching status. Details regarding the management protocol are presented in Table 1.

2.4 | Patient Characteristics

We recorded pertinent variables directly from the patient charts. These included demographics (age, gender, & race), transplant indication, pre-transplant co-morbidities, CMV serostatus, pre-transplant testing and course such as need of bridging strategies, need of cardiopulmonary bypass (CPB) during the surgery, use of induction, and early postoperative course including primary graft dysfunction (PGD) at 0 and 72 h [13], development of acute kidney injury (AKI, defined using the Risk, Failure, Loss of kidney function, and end-stage kidney disease classification [14], any need of reintubation, duration of intubation, and length of intensive care unit and hospital stay. Patients were reviewed for the development of any confirmed non-CMV infections during the first 6 months and the development of venous thromboembolism (VTE) during the 1st year after their transplant. We also recorded the development of CMV viremia and the highest viral load at any point during the post-transplant course, the spectrum of organ involvement with CMV viremia, and any CMV mutations that confer drug resistance. Finally, we collected data on the early development of CLAD (during the 3-year post-transplant) and post-transplant survival.

The diagnosis of CMV infection and invasive disease was defined per the American Society of Transplantation Infectious Disease working group on infectious diseases monitoring [15].

2.5 | Outcome Variables

The primary outcome variable was post-transplant survival. Development of CMV viremia, early CLAD, and CLAD-free 3-year survival were analyzed as secondary outcome variables.

2.6 | Statistical Analysis

The analysis used SPSS statistical software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

TABLE 1 | CMV management protocol among lung transplant patients.

CMV prophylaxis

High-risk mismatch (CMV IgG D+/R−)

1. IV ganciclovir 5 mg/kg daily × 30 days–adjusted for renal insufficiency
2. After completing IV ganciclovir, valganciclovir 450 mg PO BID indefinitely–adjusted for renal function
3. Cytomegalovirus IVIG (Cytogam) 150 mg/kg within 72 h of transplant, then at weeks 2, 4, 6, and 8 followed by 100 mg/kg at weeks 12 and 16
4. In patients with confirmed short-telomere syndrome, letermovir 480 mg PO daily could be considered primary prophylaxis.
5. Add renally-dosed valacyclovir with the use of letermovir
6. If valganciclovir is discontinued due to WBC <3.5, use letermovir 480 mg PO daily.
7. If unable to access letermovir, use GM-CSF analogs to maintain patients on valganciclovir.

Intermediate or low risk (CMV IgG D+/R+, D−/R+ D−/R−)

1. IV ganciclovir 5 mg/kg daily (adjusted for renal insufficiency) x 14 days or until discharge, whichever comes first.
2. After completing IV ganciclovir (or at discharge), valganciclovir 450 mg PO/FT BID indefinitely–adjusted for renal insufficiency
3. In patients with confirmed short-telomere syndrome, letermovir 480 mg PO daily could be considered as primary prophylaxis (add renally-dosed valacyclovir)

CMV monitoring

High-risk mismatchCMV by PCR monthly × 6 months, at 9 months, 1 year, and every 3 months thereafterNon high-risk mismatch (D−/R−, D+/R+, D−/R+)CMV by PCR monthly × 6 months, at 9 months, 1 year, and every 6 months thereafterIf CMV virus is detected on PCR:

1. If detected but not quantifiable, recheck quantitative PCR, and order CMV by PCR every 2 Weeks ×2. If it remains detected, monthly until negative. Once negative, return to the routine testing schedule
   a. Check that the valganciclovir doses are appropriate for renal function
   b. CMV detected but not quantifiable does not warrant therapeutic valganciclovir
2. If quantifiable, recheck quantitative PCR at least weekly until the virus is undetectable ×2
   a. If the patient is not on valganciclovir prophylaxis, follow the Ganciclovir (GCV) susceptible algorithm, as below.
   b. If the patient is on valganciclovir prophylaxis and the CMV PCR > 500, send the genotype and manage according to the results as below
   c. Once CMV by PCR undetectable ×2, resume normal monitoring schedule
   d. Consider checking a Cylex level
   e. Consider immunosuppression reduction

CMV treatment

Ganciclovir susceptible CMV infection

1. Reduction of Immunosuppression if feasible
2. Antivirals
   a. CMV Viremia < 3000 IU/mL: valganciclovir 900 mg PO BID (adjust based on renal functions)
   b. CMV Viremia ≥ 3000 IU/mL, CMV Enteritis, CMV Pneumonitis, patients unable to tolerate PO or symptomatic patients
3. Ganciclovir 5 mg/kg IV BID (adjust based on renal function)
4. Cytogam 150 mg/kg IV twice weekly only for patients with end-organ disease, CMV Pneumonitis, and those with refractory disease (defined as a lack of > 1 log10 reduction in CMV PCR titer in 1 week)
5. Once the CMV Viremia or CMV end-organ disease improves, and the patient able to tolerate PO—switch to valganciclovir
6. Duration of therapy
   a. CMV Viremia: For a minimum of 3 weeks and until two CMV PCR's are negative at least 1 week apart
   b. CMV Enteritis or Pneumonitis: For a minimum of 4–6 weeks and until two CMV PCR's are negative at least 1 week apart
7. Secondary Prophylaxis
   a. At completion of therapy, return to prophylactic dosing of valganciclovir

(Continues)

TABLE 1 | (Continued)

Ganciclovir resistant and refractory CMV infection

1. Consult Transplant Infectious Diseases
2. Reduction of Immunosuppression if feasible
3. Antiviral Options
   a. Maribavir 400 mg PO BID for 8 weeks.
      i Do not use for those with CNS or eye involvement
      ii Do not use in those with high viral loads, as there is a high risk of failure
   b. Cidofovir–Do not use with UL54 mutation
      i 1 mg/kg IV three times weekly until CMV PCR is negative or for 4–6 weeks in cases of CMV enteritis or pneumonitis.
      ii Probenecid 2 g PO 3 h prior to each dose
      iii Probenecid 1 g PO at 2 and 8 h after each dose
      iv Before each dose, give 1L NS bolus
   c. Foscarnet
      i Dose adjusted for renal function
      ii Pre-medication with 1 L NS bolus
4. Duration of therapy
   a. CMV Viremia: For a minimum of 2 weeks and until two CMV PCR's are negative at least 1 week apart
   b. CMV Enteritis or Pneumonitis: For a minimum of 4–6 weeks and until two CMV PCR's are negative at least 1 week apart

Initial analysis entailed comparisons of variables among the two groups formed based on recipient classification as high-risk CMV mismatch. Variables were initially evaluated in a univariate fashion using the Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables.

We then sought to investigate the possibility of an independent association of high-risk CMV mismatch status with post-transplant mortality. The study group was divided based on post-transplant survival, and variables were compared between the two groups using a similar approach. With post-transplant outcome as the dependent variable, various patient characteristics significant on univariate analysis, along with patient demographics and high-risk CMV mismatch status, were included in a Cox proportional hazard model to identify variables independently associated with post-transplant mortality.

Kaplan–Meier analysis was conducted to compare survival among recipients with and without high-risk CMV mismatch status.

Statistical significance was considered at $p < 0.05$ (two-tailed only).

3 | Results

The majority of the transplant donors (70.7%) and recipients (62.3%) were CMV seropositive. The most frequent CMV match group comprised both donor and recipient being seropositive (D+/R+ 44.8%), while double seronegative was the smallest group (D−/R− 12%). The proportion of recipients classified as high-risk CMV mismatch was 25.6% (D+/R− $n = 83$). The remaining 57 seropositive recipients received an organ from a seronegative donor (D−/R+ 17.6%).

3.1 | Clinical Course

The CMV prophylaxis and management were implemented per protocol (Table 1). Significant and recurrent leukopenia (white blood count <3500/dL on three or more occasions) was common (26.2%) and necessitated adjustment of cell cycle inhibitors along with >3 doses of GM-CSF. A switch to letermovir was needed in 10.8% of the study group.

Table 2 compares baseline and post-transplant characteristics of LT recipients with and without high-risk CMV mismatch status. Overall, there was little difference in the background profile of the two groups. However, a significantly higher proportion of the mismatch group needed bridging on mechanical ventilation (9.6% vs. 3.7%, $p = 0.04$) and extracorporeal membrane oxygenation (ECMO, 14.5% vs. 6.2%, $p = 0.035$). Regardless, the early course of the two groups was identical, with similar incidences of significant PGD and AKI. Both groups experienced a similar frequency of confirmed non-CMV infections. At 1 year, both groups had a similar incidence of VTE and had a similar degree of renal function loss. However, the mismatch group experienced a significantly higher burden of CMV viremia during their lifetime (prevalence of quantifiable CMV viremia: 32.5% vs. 10%; OR, 95% CI: 4.4, 2.34–8.13; $p < 0.001$). The median viral load among mismatch patients with CMV viremia was significantly higher (median with range: 2050, 378–115 500 vs. 518, 341–2073 IU/mL; $p = 0.03$) and more likely to develop drug resistance (14.4% vs. 0.8%; OR, 95% CI: 20.2, 4.4–92.4; $p < 0.001$). Additionally, complex mutations conferring multidrug resistance were only seen among the mismatch patients (two patients with ganciclovir and cidofovir resistance and one patient with ganciclovir, cidofovir, and foscarnet resistance). All the remaining patients (2 in non-mismatch and 9 in mismatch groups) had UL 97 mutation conferring resistance only to ganciclovir. Finally, mismatch patients were more likely to develop organ involvement with the development of CMV viremia (30.3% vs. 5.5%;

TABLE 2 | Comparative profile of patients with and without high-risk CMV mismatch status.

	High-risk CMV mismatch: No ($n = 241$)	High-risk CMV mismatch: Yes ($n = 83$)	OR (95% CI)	*p* value
Age (years)	60 (51–66)	60 (46–65)		0.45
Sex				
Male	142 (58.9%)	56 (67.5%)	0.76 (0.51–1.13)	0.19
Female	99 (41.1%)	27 (32.5%)		
Race				
Caucasian	179 (74.3%)	71 (85.5%)		0.45
African–American	29 (12%)	7 (8.4%)		
Hispanic	26 (10.8%)	4 (4.8%)		
Asian	3 (1.2%)	1 (1.2%)		
Others	4 (1.6%)			
BMI (Kg/m^2)	25.3 (21.2–28)	24.7 (21.1–27.3)		0.39
Transplant Indication				
Restrictive	134 (55.6%)	48 (57.8%)		0.76
Obstructive	68 (28.2%)	19 (22.9%)		
Suppurative	25 (10.4%)	11 (13.3%)		
Vascular	14 (5.8%)	5 (6%)		
eGFR>60 at match	221 (91.7%)	78 (94%)	0.71 (0.26–1.95)	0.64
Pre-transplant at home	197 (81.7%)	63 (75.9%)	1.42 (0.78–2.59)	0.26
Need of ECMO as BTT	9 (3.7%)	8 (9.6%)	0.36 (0.14–0.98)	**0.04**
Need of MV as BTT	15 (6.2%)	12 (14.5%)	0.54 (0.34–0.86)	**0.035**
LAS at match	42.5 (35.4–42.5)	45 (36.8–57.4)		0.11
Type of Transplant				
Right single	29 (12%)	10 (12%)		0.91
Left single	22 (9.1%)	9 (10.8%)		
Bilateral	190 (78.8%)	64 (77.1%)		
Use of CPB during transplant	91 (37.8%)	34 (41%)	0.87 (0.53–1.45)	0.69
Grade 2 or 3 PGD at 72 h	57 (23.7%)	21 (25.3%)	0.91 (0.51–1.63)	0.77
Use of basiliximab induction	147 (61%)	53 (63.9%)	0.89 (0.53–1.48)	0.7
Post-op AKI	45 (18.7%)	16 (19.3%)	0.96 (0.51–1.81)	1.0
No confirmed infections during 6 months post-transplant	79 (32.8%)	31 (37.3%)	0.82 (0.49–1.38)	0.5
VTE during the 1st year	72 (30.3%	29 (34.9%)	0.79 (0.47–1.35)	0.47
eGFR at 1-year post-transplant (mL/min per 1.73m^2)				
>60	119 (49.3%)	43 (51.9%)	1.1 (0.67–1.82)[a]	0.74
30-60	115 (47.7%)	39 (47%)		
<30	7 (2.9%)	1 (1.2%)		
Highest level of CMV viremia				
None	186 (77.2%)	50 (60.2%)	4.4 (2.34–8.13)[a]	**<0.001**
Detectable, non-quantifiable	31 (12.9%)	6 (7.2%)		
Quantifiable	24 (10%)	27 (32.5%)		

(Continues)

TABLE 2 | (Continued)

	High-risk CMV mismatch: No ($n = 241$)	High-risk CMV mismatch: Yes ($n = 83$)	OR (95% CI)	p value
Highest CMV viral load (IU/mL)	518 (341–2073)	2050 (378–115500)		**0.03**
Resistant CMV viremia	2 (0.8%)	12 (14.4%)	20.2 (4.4–92.4)	**<0.001**
Clinical presentation of CMV viremia	$n = 55$	$n = 33$		
Asymptomatic	52 (94.5%)	23 (69.7%)		**0.001**
Constitutional	1 (1.8%)	2 (6%)		
Pneumonitis	1 (1.8%)	2 (6%)		
Pneumonitis + Colitis	1 (1.8%)	4 (12.1%)		
Pneumonitis + Esophagitis		1 (3%)		
Retinitis		1 (3%)		
Post-transplant CLAD-free survival				
1 year	173 (71.8%)	63 (75.9%)	0.81 (0.45–1.44)	0.48
2 years	132 (54.8%)	44 (53%)	1.07 (0.65–1.77)	0.8
3 years	128 (53.1%)	33 (39.7%)	1.52 (0.97–2.36)	0.08
8-year survival	95 (39.4%)	32 (38.6%)	1.03 (0.7–1.51)	1.0

Abbreviations: AKI, acute kidney injury; BMI, body mass index; BTT, bridge to transplantation; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate (calculated using Chronic Kidney Disease Epidemiology (CKD-EPI) 2021 equation [16]); LAS, lung allocation score; MV, mechanical ventilation; PGD, primary graft dysfunction; VTE, venous thromboembolism.

[a]OR based on 2 × 2 comparisons with eGFR cut-off of 60 and for CMV viremia based on the development of quantifiable CMV viremia.

$p = 0.002$), with pneumonitis and colitis ($n = 4$) being the most common presentation. In contrast, the non-mismatch group was more likely to be asymptomatic at diagnosis (94.5% vs. 69.7%, $p = 0.002$).

Regardless, the two groups had similar long-term outcomes with no statistically significant difference in CLAD-free survival at various time points or overall post-transplant mortality. Kaplan–Meier analysis also showed overlapping survival curves for the two groups with similar long-term survival (Figure 1A). Additionally, the survival curves for the four groups based on the donor CMV serostatus (namely, high-risk CMV mismatch, D+/R+, D−/R+ and D−/R− groups) also showed similar long-term survival (Figure 1B).

3.2 | Survival Analysis

Table 3 lists the variables significantly associated with post-transplant mortality on univariate analysis. On Cox-proportional hazard analysis, only transplant indication was independently associated with post-transplant mortality ($p = 0.004$, Table 3). The models included CMV mismatch as one of the covariates, with and without CMV viremia. However, neither high-risk CMV mismatch nor development of CMV viremia at any time during the post-transplant period was independently associated with post-transplant mortality.

4 | Discussion

The current study reports our experience of a protocolized approach using a multimodality pharmacotherapeutic strategy to attenuate the significant risks associated with donor-derived CMV infection among high-risk mismatch patients. In addition to the lifelong use of valganciclovir for high-risk mismatch patients, our protocol included the protocolized use of CMV-specific immunoglobulin infusions, proactive surveillance, and prompt management of breakthrough CMV infections. The study group consisted of patients transplanted between 2012 and 2016 as we sought to assess the long-term impact of the management protocol and ensure a median follow-up period of 10 years.

Despite significant advances in preventing and managing direct and indirect effects from CMV infections, outcomes among high-risk CMV mismatch patients have consistently been inferior to those without [10–12]. Among patients with solid organ transplantation, the risk of donor-derived CMV infection is the highest among mismatched lung recipients. This is likely due to the size of the transplanted organ, which has a higher quantum of virus present [17, 18]. Furthermore, LT patients are maintained on a higher level of immunosuppression, given an increased risk of alloimmune processes, thereby increasing the risk of breakthrough CMV infections. This fueled the pre-emptive use of antiviral agents directed against CMV, which has risen rapidly since the early 2000s when valganciclovir became available [8]. However, despite the availability of highly effective

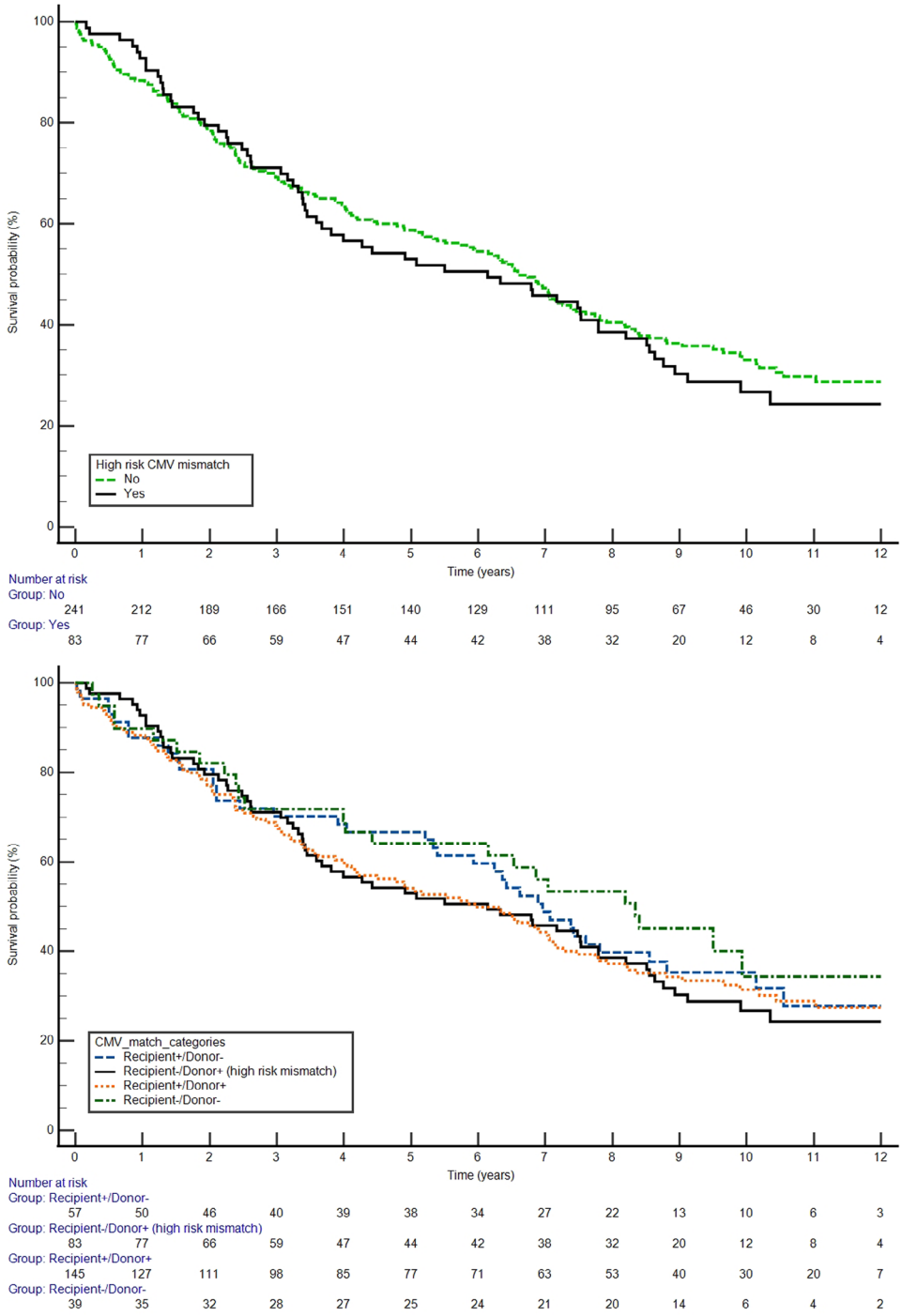

FIGURE 1 | (A) Survival curves among patients with and without high-risk CMV mismatch status ($n = 324$) showing identical long-term survival (Log Rank $p = 0.539$). (B) Survival curves among patients based on the donor CMV serostatus, namely D+/R− or high-risk CMV mismatch ($n = 83$); D+/R+ ($n = 145$), D−/R+ ($n = 57$) and D−/R− ($n = 39$) also showed similar long-term survival (Log Rank $p = 0.46$).

antiviral agents and the broader application of these agents [19–21], this difference in outcome has continued to persist. There is likely a combination of factors driving these findings. The duration of therapy has emerged as an important component of CMV prophylaxis. In a multicenter survey of CMV management practices, nearly every program utilized primary prophylaxis [9]. However, almost 90% of the programs discontinued prophylaxis by the end of the 1st year. In a single-center study, Toyoda and colleagues found that most CMV infections tended to occur after the completion of CMV prophylaxis with valganciclovir [11]. This has led to considering longer, even lifelong, prophylaxis among selected patients, although the practice has remained highly variable [10]. A significant proportion of patients may develop breakthrough CMV viremia despite being on CMV prophylaxis with valganciclovir, either due to inadequate dosing, development of resistance [22], or both in some cases. The myelosuppressive effects of valganciclovir leading to neutropenia with consequent use of colony-stimulating factors may also worsen outcomes

TABLE 3 | Variables associated with post-transplant mortality on univariate and Cox proportional hazard analysis.

	Post-transplant mortality: Yes ($n = 221$)	Post-transplant mortality: No ($n = 103$)	*p* value	Adjusted HR (95% CI)	*p* value
Age (years)	61 (51–67)	58 (47–64)	0.008	1.01 (0.99–1.03)	0.241
Race					
Caucasian	164 (74.2%)	86 (83.5%)	0.026		0.531
African–American	28 (12.7%)	8 (7.8%)			
Hispanic	25 (11.3%)	5 (4.9%)			
Asian		4 (3.8%)			
Others	3 (1.8%)				
BMI (Kg/m^2)	25.4 (21.6–28.3)	24.2 (19.4–27)	0.017	1.02 (0.98–1.06)	0.236
Transplant indication			0.012		
Restrictive	129 (58.4%)	53 (51.5%)		Reference	0.004
Obstructive	54 (24.4%)	33 (32%)		0.91 (0.65–0.1.28)	0.6
Suppurative	20 (9%)	16 (15.5%)		1.11 (0.57–2.18)	0.76
Vascular	18 (8.1%)	1 (1%)		2.775 (1.55–4.89)	0.001
Highest level of CMV viremia			0.033	1.15 (0.96–1.37)	0.14
None	150 (67.8%)	83 (82.2%)			
Detectable, non-quantifiable	29 (13.1%)	8 (7.9%)			
Quantifiable	42(19%)	10 (9.9%)			
High-risk CMV mismatch	60 (27.1%)	23 (22.3%)	0.41	0.94 (0.68–1.3)	0.717

Note: In the Cox multivariate model, post-transplant mortality was the dependent variable, and all six variables in the table were entered as covariates in the model.
Abbreviations: BMI, body mass index; CMV, cytomegalovirus.

among patients on prolonged CMV prophylaxis [23]. The use of letermovir as an alternative to valganciclovir may help address this particular issue [24]. Finally, the effects of CMV mismatch status and/or viremia may extend beyond the direct impact of the CMV virus itself [10, 25], and the use of antiviral drugs may not attenuate some of these effects. Intriguingly, regardless of the serostatus matching, CMV disease is not common as a direct cause of mortality, and most deaths among mismatched patients were attributable to CLAD [10].

The findings from the current analysis build on earlier work focused on improving outcomes among high-risk mismatch patients. Few studies thus far have demonstrated the impact of strategies aimed at mitigating high-risk CMV mismatch on long-term survival after LT. Clearly, improvement in long-term survival is an area where little progress has been made in the field of LT, and interventions ought to be judged based on harder endpoints over a longer time horizon. While the current analysis included some surrogate endpoints to capture data on safety and efficacy aspects of the regimen during the early post-transplant period, the primary goal was to determine the impact on long-term survival. This is pertinent given the potential for adverse effects of an intervention that may nullify the putative benefits of delaying or preventing CMV infection-related ill effects. While progression to CLAD or a survival benefit over a shorter time horizon may be seen with some interventions, it may not eventually translate into improved long-term survival.

The CMV prophylaxis regimen described in the current paper appeared to be well tolerated. It was not associated with an increased risk of non-CMV infections, VTE, or renal dysfunction during the early post-transplant period. The incidence of CLAD-free survival at different time points was also similar between the two groups. Furthermore, given the cumbersome protocol consisting of an extended course and the use of multiple pharmacologic agents, the favorable impact of these strategies in mitigating the risks of high-risk CMV mismatch on long-term survival was reassuring. Regardless, the current analysis does not provide insights into the potential benefits of individual components of the protocol.

The use of a prophylactic regimen in the current study appeared to mitigate the risk of quantifiable CMV infection (15.8%)and invasive disease (3.1% for the overall study group), validating the efficacy of the antiviral pharmacotherapy. The incidence of CMV infection and disease in the current cohort is clearly lower than in previous studies [11, 26]. Ruttmann and colleagues [27] studied 68 LT recipients of CMV seropositive donors and found the 3-year burden of CMV viremia of 50% and CMV disease of 26.5%. Similarly, Weill et al. [28] reported an incidence of CMV disease

of 22.1% ($n = 86$) while more than half of the patients developed CMV disease in another study ($n = 77$, 54.5%).[29] It is noteworthy that while similar pharmacologic agents were utilized, none of the earlier studies reported long-term use of any of the antiviral agents.

Despite an overall lower risk than previous studies, the high-risk mismatch group had a statistically significant higher lifetime risk of CMV viremia that was both quantitatively (increased frequency of quantifiable viremia and higher levels of viral loads) and qualitatively (resistant viremia and tissue invasive disease) significantly worse. Interestingly, though, CMV viremia did not have an independent association with long-term survival. Perhaps the early detection of CMV viremia due to the active surveillance component of the protocol led to prompt management, thereby preventing severe CMV disease. It is also possible that immune augmentation with CMV-specific immunoglobulin infusions may benefit by reducing the risk of tissue invasion and CMV disease among seronegative recipients, which has been described among patients with other solid organ transplants, including LT [29–32]. However, our analysis regarding the organ involvement among viremic patients did not demonstrate such a benefit as mismatch patients had a significantly higher risk of invasive disease.

The multimodality prophylactic regimen has potential drawbacks that may not be well-captured in the current analysis. These include an increase in the overall cost of care and the potential for infectious and thrombotic complications from the central line needed for intravenous ganciclovir during the early post-transplant period. Additionally, patients may experience adverse effects from various medications, especially with the extended use of valganciclovir. Bone marrow suppression can be especially problematic among patients with telomeropathies or marrow fragility for other reasons. An increased incidence of resistant viremia in the mismatch group may also be related to the extended use of valganciclovir. However, neither appeared to adversely impact outcomes among the mismatch group.

Future research should closely examine long-term outcomes in a multi-center study, assess the benefits and drawbacks of particular prophylactic interventions, and compare outcomes with and without prophylaxis, specifically among CMV mismatch patients.

It is concluded that the multimodality CMV management protocol described in the current report appears to be associated with improved outcomes leading to long-term survival among high-risk CMV mismatch patients to approximate the non-CMV mismatch recipients. Despite the resource-intensive nature of this protocol, the improved outcomes among high-risk mismatch patients justify its expanded use.

Author Contributions

Natasha Banga: study design, data analysis, article preparation, and approval, statistics. **Rohan Kanade**: data collection and analysis, approval of article. **Anishka Kappalayil**: data collection and analysis, approval of article. **Irina Timofte**: article preparation, approval of article. **Adrian Lawrence**: article preparation, approval of article. **Srinivas Bollineni**: article preparation, approval of article. **Vaidehi Kaza**: article preparation, approval of article. Fernando Torres: Study design, data interpretation, article preparation, critical revision of article, and approval of article.

Acknowledgments

Fernando Torres received consulting fees from Kamada Inc. No other disclosures.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. M. R. Zamora, "Cytomegalovirus and Lung Transplantation," *American Journal of Transplantation* 4 (2004): 1219–1226.

2. D. C. Chambers, W. S. Cherikh, M. O. Harhay, et al., "The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-Sixth Adult Lung and Heart-Lung Transplantation Report-2019; Focus Theme: Donor and Recipient Size Match," *Journal of Heart and Lung Transplantation* 38 (2019): 1042–1055.

3. A. G. L'Huillier, V. H. Ferreira, T. Ku, I. Bahinskaya, D. Kumar, and A. Humar, "Improving Our Mechanistic Understanding of the Indirect Effects of CMV Infection in Transplant Recipients," *American Journal of Transplantation* 19 (2019): 2495–2504.

4. D. R. Snydman, A. P. Limaye, L. Potena, and M. R. Zamora, "Update and Review: State-of-the-Art Management of Cytomegalovirus Infection and Disease Following Thoracic Organ Transplantation," *Transplantation Proceedings* 43, no. S3 (2011): S1–S17.

5. A. Roux, G. Mourin, S. Fastenackels, et al., "CMV Driven CD8(+) T-Cell Activation Is Associated With Acute Rejection in Lung Transplantation," *Clinical Immunology* 148 (2013): 16–26.

6. M. Paraskeva, M. Bailey, B. J. Levvey, et al., "Cytomegalovirus Replication Within the Lung Allograft Is Associated With Bronchiolitis Obliterans Syndrome," *American Journal of Transplantation* 11 (2011): 2190–2196.

7. C. N. Kotton, D. Kumar, A. M. Caliendo, et al., "The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation," *Transplantation* 102 (2018): 900–931.

8. M. J. Russo, D. I. Sternberg, K. N. Hong, et al., "Postlung Transplant Survival Is Equivalent Regardless of Cytomegalovirus Match Status," *Annals of Thoracic Surgery* 84 (2007): 1129–1135.

9. D. M. Zuk, A. Humar, J. G. Weinkauf, D. C. Lien, R. G. Nador, and D. Kumar, "An International Survey of Cytomegalovirus Management Practices in Lung Transplantation," *Transplantation* 90 (2010): 672–676.

10. M. Kawashima, J. Ma, E. Huszti, et al., "Association Between cytomegalovirus Viremia and Long-Term Outcomes in Lung Transplant Recipients," *American Journal of Transplantation* 24 (2024): 1057–1069.

11. T. Toyoda, C. Kurihara, T. Kaiho, et al., "Predictors of Cytomegalovirus Recurrence Following Cessation of Posttransplant Prophylaxis," *Journal of Surgical Research* 299 (2024): 129–136.

12. C. Kurihara, R. Fernandez, N. Safaeinili, et al., "Long-Term Impact of Cytomegalovirus Serologic Status on Lung Transplantation in the United States," *Annals of Thoracic Surgery* 107 (2019): 1046–1052.

13. G. I. Snell, R. D. Yusen, D. Weill, et al., "Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, Part I: Definition and Grading-A 2016 Consensus Group Statement of the International

Society for Heart and Lung Transplantation," *Journal of Heart and Lung Transplantation* 36 (2017): 1097–1103.

14. R. Bellomo, C. Ronco, J. A. Kellum, R. L. Mehta, and P. Palevsky, Acute Dialysis Quality Initiative workgroup, "Acute Renal Failure—Definition, Outcome Measures, Animal Models, Fluid Therapy and Information Technology Needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group," *Critical Care* 8 (2004): R204–R212.

15. A. Humar and M. Michaels, "American Society of Transplantation Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation," *American Journal of Transplantation* 6 (2006): 262–274.

16. L. A. Inker, N. D. Eneanya, J. Coresh, et al., "New Creatinine- and Cystatin C-Based Equations to Estimate GFR Without Race," *New England Journal of Medicine* 385 (2021): 1737–1749.

17. A. Meesing and R. R. Razonable, "New Developments in the Management of Cytomegalovirus Infection after Transplantation," *Drugs* 78 (2018): 1085–1103.

18. M. Balthesen, M. Messerle, and M. J. Reddehase, "Lungs Are a Major Organ Site of cytomegalovirus Latency and Recurrence," *Journal of Virology* 67 (1993): 5360–5366.

19. M. R. Zamora, R. D. Davis, and C. Leonard, CMV Advisory Board Expert Committee, "Management of Cytomegalovirus Infection in Lung Transplant Recipients: Evidence-Based Recommendations [Published Correction Appears in Transplantation. 2005 Aug 27;80(4):545]," *Transplantation* 80 (2005): 157–163.

20. T. G. Wreghitt, S. J. Abel, K. McNeil, et al., "Intravenous Ganciclovir Prophylaxis for Cytomegalovirus in Heart, Heart-Lung, and Lung Transplant Recipients," *Transplant International* 12 (1999): 254–260.

21. S. M. Palmer, D. C. Grinnan, B. Diane Reams, M. P. Steele, R. H. Messier, and R. Duane Davis, "Delay of CMV Infection in High-Risk CMV Mismatch Lung Transplant Recipients Due to Prophylaxis With Oral Ganciclovir," *Clinical Transplantation* 18 (2004): 179–185.

22. W. L. Drew, C. V. Paya, and V. Emery, "Cytomegalovirus (CMV) Resistance to Antivirals," *American Journal of Transplantation* 1 (2001): 307–312.

23. L. K. Tague, D. Scozzi, M. Wallendorf, et al., "Lung Transplant Outcomes Are Influenced by Severity of Neutropenia and Granulocyte Colony-Stimulating Factor Treatment," *American Journal of Transplantation* 20 (2020): 250–261.

24. A. K. Mezochow, E. Clausen, K. Whitaker, T. Claridge, E. Blumberg, and A. M. Courtwright, "Letermovir Should be First-Line Cytomegalovirus Prophylaxis in Lung Transplant Recipients," *American Journal of Transplantation* 25 (2025): 908–915.

25. T. Crough and R. Khanna, "Immunobiology of Human Cytomegalovirus: From Bench to Bedside," *Clinical Microbiology Reviews* 22 (2009): 76–98.

26. F. Rea, L. Potena, N. Yonan, F. Wagner, and F. Calabrese, "Cytomegalovirus Hyper Immunoglobulin for CMV Prophylaxis in Thoracic Transplantation," *Transplantation* 100, no. S3 (2016): S19–S26.

27. E. Ruttmann, C. Geltner, B. Bucher, et al., "Combined CMV Prophylaxis Improves Outcome and Reduces the Risk for Bronchiolitis Obliterans Syndrome (BOS) After Lung Transplantation," *Transplantation* 81, no. 10 (2006): 1415–1420.

28. D. Weill, B. J. Lock, D. L. Wewers, et al., "Combination Prophylaxis With Ganciclovir and Cytomegalovirus (CMV) Immune Globulin After Lung Transplantation: Effective CMV Prevention Following Daclizumab Induction," *American Journal of Transplantation* 3 (2003): 492–496.

29. H. A. Valantine, H. Luikart, R. Doyle, et al., "Impact of Cytomegalovirus Hyperimmune Globulin on Outcome After Cardiothoracic Transplantation: A Comparative Study of Combined Prophylaxis With CMV Hyperimmune Globulin plus Ganciclovir versus Ganciclovir Alone," *Transplantation* 72 (2001): 1647–1652.

30. D. R. Snydman, B. G. Werner, B. Heinze-Lacey, et al., "Use of Cytomegalovirus Immune Globulin to Prevent Cytomegalovirus Disease in Renal-Transplant Recipients," *New England Journal of Medicine* 317 (1987): 1049–1054.

31. D. R. Snydman, B. G. Werner, N. N. Dougherty, et al., "Cytomegalovirus Immune Globulin Prophylaxis in Liver Transplantation. A Randomized, Double-Blind, Placebo-Controlled Trial," *Annals of Internal Medicine* 119 (1993): 984–991.

32. C. Lopez Garcia-Gallo, C. García Fadul, R. Laporta, F. Portero, I. Millan, and P. Ussetti, "Cytomegalovirus Immunoglobulin for Prophylaxis and Treatment of Cytomegalovirus Infection in the (Val)Ganciclovir Era: A Single-Center Experience," *Annals of Transplantation* 20 (2015): 661–666.

Cytogam [Cytomegalovirus Immune Globulin Intravenous (Human)]

Cytogam® is an intravenous immunoglobulin containing standardized amount of antibody to cytomegalovirus.

Indication and Usage:

It is indicated for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas and heart. In transplants of these organs other than kidney from CMV seropositive donors into seronegative recipients, prophylactic CMV-IGIV should be considered in combination with ganciclovir.

Important Safety Information:

Cytogam® is contraindicated in individuals with a history of a prior severe reaction associated with the administration of this or other human immunoglobulin preparations. Persons with selective immunoglobulin A deficiency have the potential for developing antibodies to immunoglobulin A and could have anaphylactic reactions to subsequent administration of blood products that contain immunoglobulin A, including Cytogam.

Immune Globulin Intravenous (Human) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Especially in such patients, IGIV products should be administered at the minimum concentrations available and the minimum rate of infusion practicable. Those containing sucrose as a stabilizer, like Cytogam, account for a disproportionate share of the total number of reports of renal dysfunction and acute renal failure when given at daily doses of 350 mg/kg or greater.
During administration, the patient's vital signs should be monitored continuously, and careful observation made for any symptoms throughout the infusion. Epinephrine and diphenhydramine should be available for the treatment of an acute and anaphylactic reactions.

Increases in serum creatinine and blood urea nitrogen (BUN) have been observed as soon as one to two days following IGIV infusion. Progression to oliguria or anuria requiring dialysis has been observed.

Immune Globulin Intravenous (Human) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, hemolysis.

Thrombotic events have been reported in association with IGIV. Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and

benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies.

Cytogam® is derived from human plasma. As with all plasma-derived products, the risk of transmission of infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, cannot be completely eliminated.

Minor reactions, such as flushing, chills, muscle cramps, back pain, fever, nausea, vomiting, arthralgia, and wheezing, were the most frequent adverse reactions observed during the clinical trials for Cytogam.

Please see full Prescribing Information for full prescribing details.

To report SUSPECTED ADVERSE REACTIONS, contact Kamada at pharmacovigilance@kamada.com or 1-(866)-916-0077 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.