



Cytomegalovirus Prevention in Liver Transplant Recipients: A Comparative Study of Universal and Preemptive Strategies with Valganciclovir

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Abstract

Background and Objectives: Universal prophylaxis and preemptive therapy are established strategies to prevent cytomegalovirus (CMV) after liver transplantation, yet their real-world comparative performance varies by center and risk mix.

Methods: We conducted a single-center retrospective cohort of consecutive adult recipients transplanted from 2013 - 2021 in Mashhad, Iran. Exposure was the CMV-prevention strategy received (universal valganciclovir prophylaxis vs preemptive PCR-based monitoring). Primary outcomes were CMV viremia (PCR-confirmed) and CMV disease (clinical/histologic). Secondary outcomes were late-onset CMV (> 100 days post-transplant), acute rejection, and mortality. Multivariable logistic regression (and Cox proportional hazards where event dates were available) adjusted for calendar era, donor/recipient serostatus (D/R), immunosuppression regimen, monitoring protocol, age, and sex.

Results: Among 475 recipients (universal valganciclovir: 170; preemptive monitoring: 305), CMV viremia occurred in 10/170 (5.9%) vs 18/305 (5.9%) ($P = 0.993$). Among the 28 infected patients, 23 (82.1%) were male. Onset timing was < 1 month in 6 (21.4%), 1-3 months in 9 (32.1%), and > 6 months in 13 (46.4%), indicating late-onset (> 3 months) in 22/28 (78.6%) overall.

Conclusions: In this cohort, universal prophylaxis and preemptive monitoring showed no significant adjusted differences in CMV infection or disease. Given era effects and center-specific practices, policy selection should consider D/R risk, monitoring logistics, and late-onset CMV risk. Multicenter studies are warranted.

Keywords: Cytomegalovirus, Liver Transplantation, Valganciclovir, Antiviral Prophylaxis, Graft Rejection

1. Background

The Global Burden of Disease Project estimates that liver disease results in two million deaths globally each year, of which one million are attributable to liver cancer and viral hepatitis, and one million to complications from liver cirrhosis (1). Liver transplantation has become the commonly used standard treatment for individuals with liver failure during the last three decades (2). However, due to

factors like immunosuppression, malnutrition, and surgical procedures, recipients of liver transplants are especially vulnerable to various infection issues. Of these side effects, 70% of liver transplant infection cases are caused by bacterial infections, which are followed by fungal and viral infections (3).

A number of parameters, such as advanced age, biliary tract manipulation, end-stage liver disease with a score greater than 30, invasive procedures, prolonged stay in the intensive care unit (ICU), renal replacement

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therapy, and reoperation, raise the risk of infection after liver transplantation (4). The risk of infection in liver transplant recipients varies over time. During the first 12 months following transplantation, there is an increased risk of developing opportunistic infections because of increasing immunosuppression (5). But after a year, immunosuppression lessens, as does the chance of opportunistic infections (3, 5, 6). However, community-acquired infections remain a concern for transplant recipients, and recurrent cholangitis can occur in patients with recurrent cholestatic liver disease or chronic allograft failure (3, 5).

After a liver transplant, viral infections may develop from a variety of sources, such as the donor (donor-acquired infections), the recipient's own reactivation of latent viruses, hospital-acquired infections, or community-acquired infections (7, 8). Viral infections are frequently accompanied by immunosuppression. Among these viral infections, cytomegalovirus (CMV) is one of the most frequently detected pathogens following liver transplantation (9). It is expected that between 50% and 60% of liver transplant recipients have CMV infection, with 20% to 30% of patients exhibiting symptoms of infection (10). Furthermore, CMV has been associated with prolonged hospitalization, greater utilization of resources, and higher overall expenses after transplantation (11, 12).

Considering the significant direct and indirect impacts of CMV, the prevention of this infection is a crucial strategy for patients after liver transplantation. Currently, various approaches are employed to effectively control CMV infection in liver transplantation, including preemptive treatment, antiviral prophylaxis, combined approaches (continuous post-prophylaxis surveillance for CMV viremia with preemptive treatment), and CMV-specific immune-directed approaches (13-15). Nevertheless, numerous medical institutions widely employ antiviral prophylaxis and preemptive treatment as their primary approaches. Antiviral prophylaxis entails the routine prescription of antiviral medications to all transplant recipients who are susceptible to CMV disease. Typically, this medication is administered for a period of three months or longer immediately following transplantation. Conversely, preemptive treatment focuses on administering antiviral medicines exclusively to recipients who exhibit signs of CMV

viremia. The goal is to prevent CMV disease until subsequent tests confirm the absence of the virus (16, 17).

Studies on liver transplant recipients have provided inconsistent findings in terms of antiviral prophylaxis and preemptive medication for CMV prevention (18-21). While antiviral prophylaxis is extensively utilized and recommended by the American Society of Transplantation (17), late-onset CMV illness following prophylaxis discontinuation has been well established and has been associated with higher mortality in liver transplant recipients (22). Preemptive medication, on the other hand, has been found to minimize the incidence of late-onset CMV disease while also improving the immunological response to CMV (18). However, conducting the preemptive strategy has logistical challenges for health care providers and is dependent on patient participation in CMV viremia monitoring (16, 23).

It is generally accepted that valganciclovir is the preferred and standard medication for preventing CMV in organ transplant recipients (24, 25). According to the guidelines, valganciclovir can be administered both universally and preemptively in R+ (CMV seropositive) liver transplant patients. Valganciclovir should be prescribed universally only in patients with D+ (CMV seropositive) donor and R- (CMV seronegative) recipient and patients receiving antithymocyte globulin (ATG) (26). This approach is adopted by some transplant centers due to the cost and practicality constraints associated with performing frequent polymerase chain reaction (PCR) tests for all patients.

2. Objectives

Hence, the purpose of this study was to compare two methods of administering valganciclovir for CMV prevention following liver transplantation: Prophylactic use immediately after transplantation and preemptive use in confirmed cases of CMV infection. Its goal was to improve the center's protocol, as the universal method, while beneficial, may have disadvantages such as late-onset CMV (Late CMV).

3. Methods

3.1. Study Design and Setting

This single-center retrospective cohort was conducted at Montaserieh Hospital, Mashhad, Iran, a tertiary referral transplant center affiliated with Mashhad University of Medical Sciences. The study covered liver transplants performed from January 2013 through December 2021, with outcome ascertainment based on routine post-transplant surveillance and electronic medical records.

3.2. Participants

We included all consecutive adult (≥ 18 years) liver transplant recipients who underwent transplantation at Montaserieh Hospital, Mashhad, Iran, between January 2013 and December 2021. Eligible patients had sufficient records to ascertain the CMV prevention strategy (universal valganciclovir prophylaxis vs preemptive PCR-guided therapy), CMV outcomes (viremia and/or disease), and core covariates (age, sex, calendar year, donor/recipient CMV serostatus where available, immunosuppression, and monitoring protocol details). We excluded patients who died within 7 days of transplantation, underwent re-transplantation during the index admission, had multi-organ transplantation, or lacked essential exposure/outcome data. Patients receiving non-valganciclovir CMV strategies were rare; they were included and categorized when documentation permitted, with a sensitivity analysis excluding them. Follow-up continued until the first CMV event, death, or last documented clinic/laboratory visit within the study window.

3.3. Exposure: Cytomegalovirus Prevention Strategy

The exposure was the center's CMV prevention strategy at the time of transplantation, classified per recipient as universal valganciclovir prophylaxis or preemptive PCR-based monitoring. Universal prophylaxis consisted of postoperative oral valganciclovir with renal dose adjustment for an institutionally defined duration; the actual duration received was abstracted from charts. The preemptive approach entailed scheduled quantitative CMV PCR surveillance with initiation of antiviral therapy upon prespecified copy-number thresholds according to institutional guidelines. In total, 170 recipients received universal prophylaxis and 305 received preemptive monitoring.

3.4. Laboratory Monitoring

Whole-blood CMV DNAemia was quantified by the hospital virology laboratory using validated real-time quantitative PCR platforms under routine internal quality control and external proficiency testing. Assay characteristics, sampling intervals, and treatment thresholds were those in force at the time and were extracted from records when available. Documented protocol modifications across years were recorded and considered in era-adjusted analyses.

3.5. Immunosuppression and Supportive Care

Induction and maintenance immunosuppression followed institutional practice and clinician judgment, typically calcineurin inhibitor-based combinations with steroids and/or antimetabolites, with lymphocyte-depleting agents reserved for selected cases. Where available, markers of immunosuppression intensity were abstracted for adjustment.

3.6. Outcomes

Primary outcomes were CMV viremia, defined as PCR-confirmed DNAemia above the laboratory quantitative threshold, and CMV disease, defined as CMV syndrome or tissue-invasive disease according to guideline-concordant clinical and, when applicable, histopathologic criteria. Secondary outcomes included late-onset CMV, defined as a first CMV event occurring more than 100 days after transplantation, biopsy-proven or clinically adjudicated acute rejection, and all-cause mortality at 90 and 180 days.

3.7. Covariates

From registries and electronic records, we abstracted age, sex, transplant calendar year (to account for era effects), donor/recipient CMV serostatus when available, primary liver disease and major comorbidities, renal function relevant to valganciclovir dosing, immunosuppression regimen and intensity, details of the monitoring protocol (sampling frequency and treatment threshold), and dates of CMV events, rejection, and death. Planned and actual durations of valganciclovir were recorded in the universal group.

3.8. Risk of Bias and Confounding Control

Because allocation to prevention strategy was nonrandom and overlapped with calendar time, we prespecified adjustment for era to mitigate confounding by evolving practices. We further addressed confounding by indication and surveillance differences by adjusting for donor/recipient serostatus, immunosuppression intensity, and monitoring protocol, in addition to age and sex. Sensitivity analyses excluded strategy-transition years and repeated models in the high-risk D+/R- subgroup where serology was documented. Missing covariate data were handled primarily by complete-case analysis, with planned sensitivity checks.

3.9. Sample Size Rationale

This was an archive-based analysis of all eligible transplants ($N = 475$) performed between 2013 and 2021. No a priori sample size calculation was performed; the precision of effect estimates is reflected in 95% confidence intervals.

3.10. Statistical Analysis

Baseline characteristics are summarized as mean $\pm$ SD or median (IQR) for continuous variables and as counts (percentages) for categorical variables; group comparisons between universal ($n = 170$) and preemptive ($n = 305$) strategies are descriptive (t -test or Mann-Whitney U; χ^2 or Fisher's exact test as appropriate). Primary inferential analyses use multivariable logistic regression to estimate adjusted associations (aOR, 95%CI) between prevention strategy and CMV viremia/disease, minimally adjusting for calendar era, donor/recipient serostatus, immunosuppression intensity, monitoring protocol, age, and sex. Where event dates are available, time-to-event methods – Kaplan-Meier with log-rank tests and Cox proportional hazards models (aHR, 95%CI) – are applied for time to first CMV event and mortality, with proportional hazards assumptions assessed. Secondary analyses evaluate late-onset CMV, acute rejection, and 90/180-day mortality with analogous models. Two-sided $P < 0.05$ denotes statistical significance. Analyses were performed in SPSS 26.

3.11. Ethics and Reporting

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences

IR.MUMS.MEDICAL.REC.1400.737, with a waiver of informed consent due to the retrospective design and minimal risk.

4. Results

4.1. Cytomegalovirus Infection: Universal Versus Preemptive Valganciclovir and Patient Characteristics

During the study period, a total of 475 patients who underwent liver transplantation were examined. Among them, 170 patients (35.8%) received valganciclovir as prophylaxis immediately after liver transplantation (universal group), while 305 patients (64.2%) received valganciclovir preemptively following a positive result on a quantitative PCR test (Table 1). Of the total number of patients, 28 were diagnosed with CMV infection, with 18 patients (5.9%) from the preemptive group and 10 patients (5.9%) from the universal group ($P = 0.993$).

Among the CMV -infected patients, 23 were male (82.1%) and 5 were female (17.9%) (Figure 1). The timing of CMV infection was less than 1 month in 6 patients (21.4%), between 1 and 6 months in 9 patients (32.1%), and more than 6 months in 13 patients (46.4%).

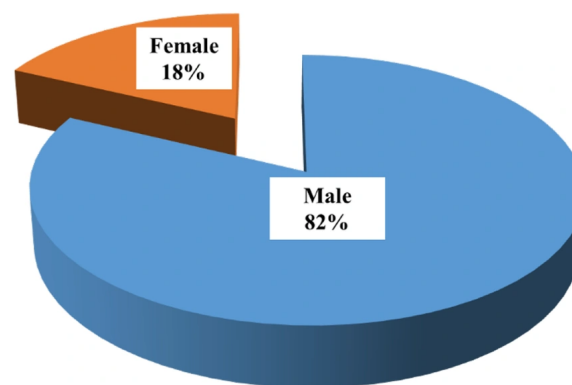


Figure 1. Distribution of cytomegalovirus (CMV) infections by gender

The average age at transplantation for patients who received valganciclovir preemptively was 44.5 ± 13.8 years, while the average age for patients who received universal valganciclovir was 27.5 ± 19.32 years ($P = 0.012$).

Table 1. Comparison of Different Variables Between Two Methods of Valganciclovir Administration ^{a,b}

Variables	Administration Method		P-Value ^b
	Preemptive	Universal	
CMV			0.993
Negative	287 (94.1)	160 (94.1)	
Positive	18 (5.9)	10 (5.9)	
Gender			0.825
Female	3 (16.7)	2 (20.0)	
Male	15 (83.3)	8 (80.0)	
Graft rejection			0.615
No	13 (72.2)	7 (70.0)	
Yes	5 (27.8)	3 (30.0)	
Time of infection with CMV (mon)			0.707
Fast (<1)	3 (16.7)	3 (30.0)	
Medium (1-6)	6 (33.3)	3 (30.0)	
Late (>6)	9 (50.0)	4 (40.0)	
Patient status			0.144
Recovery and discharge	14 (77.8)	5 (50.0)	
Personal satisfaction	0 (0.0)	2 (20.0)	
Death	3 (16.7)	3 (30.0)	
Unknown	1 (5.6)	0 (0.0)	
Cause of death			0.445
Alive	14 (77.8)	7 (70.0)	
Acute lymphocytic leukemia	0 (0.0)	1 (10.0)	
Liver transplant	2 (11.1)	1 (10.0)	
Lung infections	1 (5.6)	0 (0.0)	
Multiple organ failure	0 (0.0)	1 (10.0)	
Unknown	1 (5.6)	0 (0.0)	
Simultaneous opportunistic infection types			0.414
Negative	15 (83.3)	7 (70.0)	
Bacterial	2 (11.1)	2 (20.0)	
Viral	1 (5.6)	0 (0.0)	
Fungal	0 (0.0)	1 (10.0)	
EBV PCR			0.716
Negative	16 (88.9)	9 (90.0)	
Positive	2 (11.1)	1 (10.0)	
TB PCR			0.357
Negative	18 (100.0)	9 (90.0)	
Positive	0 (0.0)	1 (10.0)	
Blood culture			0.249
Negative	11 (61.1)	4 (40.0)	
Positive	7 (38.9)	6 (60.0)	
IgG CMV			0.037
Negative	0 (0.0)	3 (30.0)	
Positive	18 (100.0)	7 (70.0)	
IgG EBV			0.181
Negative	3 (16.7)	4 (40.0)	
Positive	15 (83.3)	6 (60.0)	
PPD test			0.448
Negative	17 (94.4)	10 (100.0)	
Positive	1 (5.6)	0 (0.0)	

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; IgG, immunoglobulin G; PCR, polymerase chain reaction; PPD, purified protein derivative; TB, tuberculosis.

^a Values are expressed as No. (%).^b Chi-squared test

4.2. Underlying Diseases

Among the patients included in the study, various underlying diseases were identified. Specifically, 7 patients (25.0%) had autoimmune hepatitis, 6 patients

(21.4%) had cryptogenic hepatitis, 4 patients (14.3%) had hepatitis B, 3 patients (10.7%) had liver cell carcinoma, 2 patients (7.1%) had oxalosis, 1 patient (3.6%) had drug hepatitis, 1 patient (3.6%) had primary sclerosing cholangitis, 1 patient (3.6%) had Wilson's disease, and 1

patient (3.6%) had hemochromatosis. The type of underlying disease was unknown for 2 patients (7.1%) (Table 2).

Table 2. Frequency of Patients with Cytomegalovirus Infection According to Underlying Diseases

Variables	No (%)
AIH	7 (25.0)
Cryptogenic	6 (21.4)
HBV	4 (14.3)
HCC	3 (10.7)
Oxalosis	2 (7.1)
Drug Induce	1 (3.6)
PSC	1 (3.6)
Wilson	1 (3.6)
Hemochromatosis	1 (3.6)
Unknown	2 (7.1)
Total patients	28 (100.0)

Abbreviations: AIH, autoimmune hepatitis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis

4.3. The Relationship Between the Type of Valganciclovir Administration Method and the Size of the Studied Variables

According to the data presented in Table 1, among the patients who received preemptive valganciclovir, 3 (16.7%) were women, while 15 (83.3%) were men. Similarly, 2 (20%) of the patients who received valganciclovir universally were women, while the remaining (80%) were men. Statistical analysis revealed no significant association between the patients' gender and the type of valganciclovir administration method ($P > 0.05$).

In patients who received valganciclovir preemptively, 5 cases (27.8%) of graft rejection were observed, while in patients who received valganciclovir universally, 3 cases (30.0%) of graft rejection were observed. Statistical analysis revealed no significant relationship between transplant rejection and the type of valganciclovir administration method ($P > 0.05$).

The results indicate that among patients who received valganciclovir preemptively, 3 individuals (16.7%) were infected with CMV within less than 1 month, 6 individuals (33.3%) between 1 and 6 months, and 9 individuals (50.0%) beyond the 6-month period. On the other hand, in the universal prescription method, 3 individuals (30.0%) were infected within less than 1 month, 3 individuals (30.0%) between 1 and 6 months, and 4 individuals (40.0%) beyond the 6-month period.

Comparison of the time of CMV infection between the two valganciclovir administration methods did not reveal a statistically significant difference ($P > 0.05$).

The information provided in Table 1 indicates that among the patients who received preemptive valganciclovir, 14 individuals (77.8%) were discharged, 3 individuals (16.7%) died, and the condition of 1 individual (5.6%) was unclear. In the group of patients who received universal valganciclovir, 5 individuals (50%) were discharged, 2 individuals (20%) were discharged based on personal consent, and 3 individuals (30%) died. Statistical analysis revealed no significant relationship between the patient's status in terms of discharge, personal satisfaction, and death in the two groups ($P > 0.05$).

As mentioned previously, among patients who received the preemptive administration method, 3 individuals (16.7%) died. The causes of death were identified as liver transplant complications in 2 individuals (11.1%) and lung infection in 1 individual (5.6%). Additionally, the cause of death remained unknown for 1 individual (5.6%). Among patients who received the universal prescription method, 3 individuals (30%) died, with causes attributed to acute lymphocytic leukemia in 1 individual (10.0%), liver transplant complications in 1 individual (10.0%), and multiple organ failure in 1 individual (10.0%). Statistical analysis revealed no significant difference in the cause of death between the two groups with preemptive and universal prescription methods ($P > 0.05$).

In patients who received preemptive administration, 2 individuals (11.1%) developed bacterial opportunistic infections, while 1 individual (5.6%) developed a viral opportunistic infection. Similarly, among patients who received universal administration, 2 individuals (20.0%) experienced bacterial opportunistic infections, and 1 individual (10.0%) developed a fungal opportunistic infection. Statistical analysis did not reveal a significant relationship between the type of opportunistic infection in the two groups ($P > 0.05$).

The information provided in Table 1 indicates that among patients who received preemptive administration, 16 individuals (88.9%) had negative Epstein-Barr virus PCR results, while 2 individuals (11.1%) had positive Epstein-Barr virus PCR results. Similarly, among patients who received universal valganciclovir, 9 individuals (90.0%) had negative Epstein-Barr virus PCR

results, and 1 individual (10.0%) had a positive Epstein-Barr virus PCR result. Statistical analysis revealed no significant relationship between the results of the Epstein-Barr virus PCR test between the two groups ($P > 0.05$).

The Tuberculosis PCR test was negative in all patients (100%) who received the preemptive administration method, while it was positive in only one patient (10.0%) who received the universal administration method. There was no statistically significant difference in the Tuberculosis PCR test results between the two groups ($P > 0.05$).

The results presented in Table 1 demonstrate that the blood culture results were negative in 11 individuals (61.1%) of patients who received preemptive administration, while they were positive in 7 individuals (38.9%). Additionally, among the patients who received valganciclovir universally, the blood culture result was negative in 4 individuals (40.0%) and positive in 6 individuals (60.0%). There was no statistically significant difference in the blood culture results between the two groups ($P > 0.05$).

The result of the CMV IgG test was positive in all patients (100%) who received the preemptive administration method. Additionally, among patients who received the universal administration method, the CMV IgG test was positive in 7 individuals (70.0%) and negative in 3 individuals (30.0%). There was a statistically significant correlation between the CMV IgG test results in the two groups ($P < 0.05$).

According to the results of Table 1, the IgG Epstein-Barr virus test result was negative in 3 patients (16.7%) who received the preemptive administration method and positive in 15 patients (83.3%). Additionally, among patients who received the universal administration method, 4 individuals (40.0%) had negative IgG Epstein-Barr virus results, while 6 individuals (60.0%) had positive IgG Epstein-Barr virus results. There was no statistically significant difference in the IgG Epstein-Barr virus test results between the two groups ($P > 0.05$).

The purified protein derivative (PPD) test result was negative in 17 patients (94.4%) who received the preemptive administration method, and it was positive in only 1 patient (5.6%). Additionally, the PPD test result was negative in all patients (100%) who received the universal administration method. There was no

significant difference in terms of the PPD test results between the two groups with preemptive and universal administration methods ($P > 0.05$).

The results of blood factor tests between the preemptive and universal administration methods of valganciclovir are presented in Table 3. Based on the analysis, a statistically significant difference was observed in the hemoglobin levels and the total types of bilirubin between the two groups ($P < 0.05$).

5. Discussion

Cytomegalovirus disease is a prevalent infectious complication following liver transplantation, necessitating a well-structured management approach that includes prevention, early detection, and appropriate treatment to ensure positive outcomes for both the patient and the transplant itself. Ganciclovir and valganciclovir are currently considered the preferred medications for preventing and treating CMV in recipients of hematopoietic cell transplantation and organ transplants. Therefore, in this study, our team aimed to compare the incidence of CMV infection in liver transplant recipients who received valganciclovir prophylaxis immediately after transplantation (universal approach) and those who underwent preemptive testing using quantitative PCR and received treatment upon a positive result.

The results obtained from this study showed that there is no statistically significant relationship between CMV infection in the two groups with preemptive and universal administration methods. The mean age of transplantation in patients who received valganciclovir preemptively was significantly higher than the group that received valganciclovir universally. The number of graft rejections in patients who received preemptive valganciclovir was higher than in those who received universal valganciclovir, but this difference was not statistically significant. The mortality rate was the same in both groups, and there was no significant difference in terms of discharge, personal satisfaction, and death between the patients in the two groups. The data of the CMV IgG test was positive in all patients (100%) who received the preemptive administration method. On the other hand, in patients with the universal administration method, the result of the CMV IgG test was positive in 7 individuals (70%) and negative in 3 individuals (30%). There was also a statistically

Table 3. Comparison of Blood Factor Test Results Between Two Methods of Valganciclovir Administration

Variables/Administration Method	N	Mean $\pm$ SD	P-Value ^a
WBC			0.231
Preemptive	18	7.64 $\pm$ 4.76	
Universal	9	5.49 $\pm$ 3.01	
Hb			0.007
Preemptive	18	11.59 $\pm$ 2.45	
Universal	9	8.72 $\pm$ 2.19	
PLT			0.914
Preemptive	18	130.83 $\pm$ 106.88	
Universal	9	125.77 $\pm$ 127.14	
BUN			0.248
Preemptive	18	21.40 $\pm$ 21.89	
Universal	10	32.20 $\pm$ 25.39	
Cr			0.465
Preemptive	18	57.57 $\pm$ 239.44	
Universal	10	0.93 $\pm$ 0.52	
ALT			0.624
Preemptive	18	231.11 $\pm$ 441.57	
Universal	10	156.30 $\pm$ 230.05	
AST			0.685
Preemptive	18	200.55 $\pm$ 405.62	
Universal	10	143.00 $\pm$ 235.83	
ALP			0.094
Preemptive	18	385.50 $\pm$ 312.84	
Universal	10	669.70 $\pm$ 557.45	
BiliTotal			0.031
Preemptive	18	2.34 $\pm$ 2.39	
Universal	9	8.41 $\pm$ 10.90	
BiliDirect			0.694
Preemptive	18	8.22 $\pm$ 29.44	
Universal	9	4.25 $\pm$ 5.20	
Na			0.536
Preemptive	16	134.93 $\pm$ 4.63	
Universal	10	136.20 $\pm$ 5.51	
K			0.79
Preemptive	16	4.20 $\pm$ 0.75	
Universal	10	4.11 $\pm$ 0.80	

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BiliDirect, direct bilirubin; BiliTotal, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; Hb, hemoglobin; PLT, platelet count; SD, standard deviation; WBC, white blood cell count.

^a Independent sample *t*-test.

significant correlation between the CMV IgG test results in the two groups.

No significant statistical relationship was observed between any of the variables, including gender, time of infection with CMV, cause of death, type of simultaneous opportunistic infection, Epstein-Barr virus PCR test result, Tuberculosis PCR test result, blood culture result, Epstein-Barr virus IgG test result, and PPD

test result. The mean hemoglobin among patients who received preemptive valganciclovir was significantly higher than the group who received universal valganciclovir. Additionally, the mean total bilirubin in patients with the universal administration method was significantly higher than in patients with the preemptive administration method.

Our study revealed that out of a total of 28 patients, 18 received preemptive valganciclovir while 10 received universal valganciclovir, resulting in CMV infection. However, our analysis indicated that there was no statistically significant relationship between CMV infection and the administration methods of preemptive and universal. Yadav et al. demonstrated in their review study that the incidence of CMV infection and CMV disease among liver transplant recipients using antiviral prophylaxis and preemptive treatment was 24.7% versus 40.4% and 6.4% versus 9.4%, respectively. This meta-analysis revealed a significant reduction in the occurrence of CMV infection due to antiviral prophylaxis compared to preemptive treatment in the high-risk group. However, there was no significant difference in the occurrence of CMV disease between the two interventions (16). Mengelle et al. also reported that the risk of CMV infection was 4.26 times higher in patients who did not receive antiviral prophylaxis after liver transplantation (27). Similarly, Florescu et al. obtained similar results in their meta-analysis (28). As a result, it seems appropriate to use antiviral prophylaxis rather than preemptive therapy in the early post-transplant period. Furthermore, prompt antiviral therapy following liver transplantation can lower the risk of other viral infections such as Epstein-Barr virus, herpes simplex virus, and respiratory syncytial virus (29). It has also been found that antiviral prophylaxis resulted in a considerably greater incidence of CMV disease in high-risk liver transplant recipients compared to preemptive therapy (19% vs. 9%) (18). Furthermore, Hui et al. discovered a significant difference in the occurrence of CMV infection and disease between antiviral prophylaxis and preemptive treatment in 1091 liver transplant recipients (30), which opposes the findings of the current research.

The contradiction between our results and previous findings may be attributed to several factors. Firstly, differences in study design, patient characteristics, and sample size could contribute to variations in results. Our study might have had a smaller sample size or different patient population, which could influence the statistical significance of the observed relationships. Secondly, the retrospective nature of our study could introduce potential biases or limitations in data collection and analysis. Inaccuracies or missing information may have affected the statistical associations between variables. Furthermore, variations

in the administration protocols of antiviral medications, such as dosages or timing, between different studies could impact the outcomes and potentially lead to different conclusions. It is also important to consider that the field of liver transplantation and management of CMV infection is evolving, and new studies and findings may provide updated information that could differ from previous research. Hence, further research with larger sample sizes, prospective designs, and standardized protocols is necessary to better understand the relationship between CMV infection, administration methods, and other variables in liver transplant recipients.

The majority of previous studies have consistently demonstrated that the mean time to the onset of CMV infection and disease in liver transplant recipients is longer with antiviral prophylaxis than with preemptive therapy. This suggests that antiviral prophylaxis delays the onset of CMV infection and disease, which can be seen as a positive impact of antiviral treatment. However, delayed onset of CMV disease after antiviral treatment is seen as a disadvantage due to the accompanying mortality (16, 19, 20). These findings contradict the results of the current investigation, which found that 50% and 40% of patients using preemptive and universal prescription methods, respectively, were infected with CMV within 6 months or more.

Our study revealed that there was no significant difference between the two strategies in terms of graft rejection and opportunistic infections. This finding is consistent with Yadav et al.'s study, which also found no significant difference in graft loss, opportunistic infections, and mortality between the two interventions (16). Similarly, Hui et al. reported no significant difference in the occurrence of other opportunistic infections between these two strategies (30). These consistent results across studies suggest that both antiviral prophylaxis and preemptive therapy are comparable in their impact on graft rejection and the occurrence of opportunistic infections.

5.1. Limitations

The retrospective nature of the study may introduce biases and limitations in data collection and analysis, potentially impacting the accuracy and reliability of the results. The relatively small sample size limits the

statistical power and generalizability of the findings. Missing or incomplete data due to the study design could further affect the results. Patient characteristics and differences in immunosuppression protocols and comorbidities may introduce confounding factors that influence the outcomes. The absence of randomization introduces selection bias and potential unmeasured confounders.

5.2. Conclusions

In a nine-year, single-center cohort of 475 liver transplant recipients, universal valganciclovir prophylaxis and preemptive PCR-guided monitoring yielded comparable crude CMV viremia rates (5.9% each), while late-onset events were common. These findings favor center-tailored prevention policies that account for serostatus mix, immunosuppression intensity, and monitoring logistics, coupled with deliberate post-prophylaxis surveillance. Larger, era-adjusted multicenter studies are needed to define when extended prophylaxis or intensified late monitoring confers the greatest benefit.

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Footnotes

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