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Pre-transplant CMV and EBV seroprevalence in liver transplant candidates in northern Iran

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ABSTRACT

Viral infections, such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV), contribute to the low survival rates of liver transplant patients. This study aimed to assess the prevalence of CMV and EBV infections in patients awaiting liver transplantation. Utilizing a census sampling approach, this cross-sectional study examined all cases of viral infections from 2016 to 2021 among liver transplant patients referred to Rasht liver transplant center, the North of Iran. The diagnosis of a recent primary viral infection was established by IgM positivity. In total, 34 individuals with a mean age of 48.9±12.2 years were included in the study. Of these, 40 individuals (59.7%) were male. The prevalence of CMV IgM and IgG antibodies among liver transplant candidates was 7.5%, and 97%, respectively. Also, the prevalence of EBV IgM and IgG antibodies was 7.5%, and 97%, respectively. The average serum vitamin D level in CMV IgM-negative patients was 30.7±17.2 compared to 55.1±22.1 in CMV IgM-positive patients ($p = 0.011$). The prevalence of active CMV and EBV infections in liver transplant patients was found to be 7.5%. These results highlight the necessity for continuous and effective strategies to prevent infection-related complications through prompt diagnosis and treatment, which are crucial for positive liver transplant outcomes.

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1. Introduction

Liver transplant recipients face numerous challenges, both immediate and long-term post-transplantation. Short-term issues can be categorized into technical complications, such as venous thrombosis and biliary disorders, and medical concerns, including infections and acute transplant rejection [1]. Post-liver-transplant infections have emerged as a primary cause of morbidity and mortality, exceeding acute rejection rates, despite advancements in surgical techniques and immunosuppressive therapies [2, 3].

Post-transplant infections are classified as either early or late, with late infections predominantly resulting from immunosuppressive drug effects, whereas early infections have alternative etiologies [3]. Enhancing our understanding of prevalent post-transplant infections and their risk factors will facilitate the development of strategies to mitigate these risks and prevent subsequent infections. Multiple independent risk factors contribute to the development of bacterial, fungal, and viral infections following transplantation. Multiple risk factors for increased post-transplant infection risk have been identified in studies. The majority of studies found prolonged operation time, extended hospitalization post-transplant, and elevated Model for End-Stage Liver Disease (MELD) scores as significant predictors of infection risk [4-6]. The MELD scoring system is favored over the Child-Turcotte-Pugh (CTP) system for patient classification and outcome prediction post-liver transplantation [7–9]. Additionally, intraoperative transfusions, particularly of Fresh Frozen Plasma (FFP) and packed red blood cells, are recognized as post-liver-transplant infection risk factors [10, 11].

Cytomegalovirus (CMV), a member of the herpesvirus family, is a significant pathogen in organ transplant recipients, affecting approximately 50-60% of this population [12–15]. It is the most significant virus that can infect humans and can cause a range of severe clinical syndromes, including fever, leukopenia (mononucleosis-like syndrome), hepatitis, pneumonitis, pancreatitis, colitis, meningoencephalitis, and gastrointestinal bleeding in immunocompromised individuals, including organ transplant recipients [16]. Around 6% of healthy adults are asymptomatic carriers of CMV [17], and nearly two-thirds of transplant recipients have pre-existing immunity, indicated by serum anti-CMV IgG antibodies [18]. The virus is transmissible via sexual or respiratory routes, blood transfusions, and from mother to child during birth or breastfeeding. Transplant recipients with positive anti-CMV IgG antibodies are at risk for latent virus reactivation, typically between 1-4 months post-transplantation [16, 18]. This reactivation is influenced by the preoperative serostatus of both the recipient and donor, as well as the type and dosage of immunosuppressive medications used [19]. The administration of anti-T cell antibodies, high-dose corticosteroids, and Mycophenolate mofetil have been associated with increased disease severity [20]. Some clinical studies have also suggested a link between CMV infection and graft rejection, with Schnitzler et al. reporting that mortality rates were 2.5 times higher in patients with pre-transplant CMV antibodies who did not receive ganciclovir prophylaxis compared to those who did [21]. Another contributor to these infections is the Epstein-Barr virus (EBV). EBV, a ubiquitous human virus found worldwide, typically spreads through bodily fluids, especially saliva, and can cause infectious mononucleosis. EBV infection can exacerbate immune system suppression, especially when combined with immunosuppressive drug therapy. Some researchers posit that EBV infection may disrupt and stimulate the immune system, increasing the risk of transplant rejection [4]. It is estimated that 80 to 90 percent of transplant recipients develop a secondary EBV infection within the first year following transplantation, which closely correlates with graft dysfunction [5]. EBV reactivation can provoke an immune response, potentially leading to transplant rejection. In some cases, increased immunosuppression to counteract rejection may result in patient mortality, highlighting the clinical significance of monitoring EBV infection [22]. Research conducted at the Pasteur Institute of Iran virology department, as well as a study on EBV infection in Tehran children and adults, suggest that approximately 80% of transplant recipients are affected by EBV [23]. Kenagy's study in the United States reported an incidence of secondary EBV infection of 17.4% within one year following transplantation. The study results indicated that 33% of the patients exhibited positive serology [24]. However, Acott's Canadian research observed EBV reactivation in 12.5% of patients experiencing acute graft rejection [25]. Shahinian et al. indicated that primary EBV infection might play a pathogenic role in some cases of post-transplant lymphoproliferative disorder (PTLD) [26].

Given the growing reliance on liver transplantation as a treatment for liver disease, meticulous attention to transplant candidates' care is imperative both pre- and post-transplantation. Viral infections, notably CMV and EBV, are recognized as factors that diminish liver transplant survival rates. Therefore, this study aimed to investigate the pre-transplant CMV and EBV seroprevalence in liver transplant candidates in northern Iran. Comprehending the influence of viral infections on the survival of liver transplants can enhance patient longevity and transplant success rates, and these insights can be useful for the management of liver transplant recipients, particularly in the Guilan province.

2. Materials and Methods

2.1 study design and data collection

This cross-sectional analytical study was conducted at the Liver Transplant Center of Razi Hospital, located in Guilan Province, Northern Iran. The study population

included patients listed for liver transplantation who were evaluated at the center between 2016 and 2021. A total of 120 liver transplant candidates were assessed for the presence of Cytomegalovirus (CMV) and Epstein–Barr Virus (EBV) infections. The Research Ethics Committee of Guilan University of Medical Sciences approved all processes of the current study (IR.GUMS.REC.1401.310). Informed consent obtained from all of the participants by signing a form in a written format. Data were collected using a census sampling method, including all eligible patients during the study period. Demographic and clinical information such as age, gender, and medication history was extracted from the hospital's medical records. Patients with incomplete clinical or laboratory data were excluded from the analysis. Laboratory parameters, including CMV and EBV serology results were retrieved from medical records. These results were used to determine the pre-transplant infection status of each patient.

2.2 Data Analysis

In this study, descriptive statistics, including mean, standard deviation, frequency, and percentage, were used to summarize the data. To assess the normality of the data distribution, the Shapiro–Wilk test and the examination of skewness and kurtosis indices were applied. Additionally, the Levene's test was used to assess the homogeneity of variances across groups. For inferential analysis, the independent samples t-test was employed for continuous variables when parametric assumptions were met. For categorical variables, or when assumptions were not met, the Fisher's exact test was applied. All statistical analyses were performed using SPSS software version 24 (IBM Corp., Armonk, NY), with a significance level set at $p < 0.05$ for all tests.

3. Results

The study evaluated 67 individuals with a mean age of 48.9±12.2 years (ranging from 18 to 69 years old). Of these participants, 40 (59.7%) were male, and the rest were female. The frequency of CMV infection, with CMV IgM and IgG positivity rates among liver transplant candidates being 7.5% (n=5) and 97% (n=65), respectively. The study found that five (7.5%) and 65 (97%) liver transplant candidates were positive for EBV IgM and IgG, respectively. According to the results, among liver transplant candidates aged below 52 years, the frequency of patients with CMV IgM-positive and CMV IgG-positive status was 2 individuals (1.6%) and 31 individuals (93.9%), respectively. In the age group of 52 years and above, the frequency of CMV IgM-positive and CMV IgG-positive cases was 3 individuals (8.8%) and 34 individuals (100%), respectively. However, the prevalence of CMV infection, based on both IgM ($p = 0.999$) and IgG ($p = 0.239$) markers, showed no statistically significant difference between the two age groups. According to the findings, among patients aged below 52 years, the frequency of EBV IgM-positive and EBV IgG-positive cases was 3 individuals (9.1%) and 32 individuals (97%), respectively. In the age group of 52 years and above, the frequency of EBV IgM-positive and EBV IgG-positive cases was 2 individuals (5.9%) and 33 individuals (97.1%), respectively. The prevalence of EBV infection, based on both IgM ($p = 0.673$) and IgG ($p = 0.999$), showed no statistically significant difference between the two age groups. According to the results, among male liver transplant candidates, the frequency of CMV IgM-positive and CMV IgG-positive cases was 3 individuals (7.5%) and 38 individuals (95%), respectively. Among female candidates, the frequency of CMV IgM-positive and CMV IgG-positive cases was 2 individuals (7.4%) and 27 individuals (100%), respectively. The prevalence of CMV infection, based on both IgM ($p = 0.999$) and IgG ($p = 0.512$), showed no statistically significant difference between male and female patients. According to the results, among male liver transplant candidates, the frequency of EBV IgM-positive and EBV IgG-positive cases was 1 individual (2.5%) and 39 individuals (97.5%), respectively. Among female candidates, the frequency of EBV IgM-positive and EBV IgG-positive cases was 4 individuals (14.8%) and 26 individuals (96.3%), respectively. The prevalence of EBV infection, based on both IgM ($p = 0.149$) and IgG ($p = 0.999$), showed no statistically significant difference between male and female patients. The detailed results of serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium, vitamin D, and albumin according to viral infection status are presented in Table 1. Notably, the mean serum vitamin D level was 55.1 ± 22.1 ng/mL in those who were CMV IgM-positive, and 30.7 ± 17.2 ng/mL in patients who were CMV IgM-negative with a statistically significant difference ($p = 0.011$).

Table 1. The detailed results of serum level of AST, ALT, calcium, and vitamin D based on viral infection

Variable	Viral infection	Test result	Mean ± SD	Test statistic	P value
AST (U/L)	CMV				
	IgM	Negative Positive	70.85 ± 55.74 71.20 ± 69.47	0.01	0.990
	IgG	Negative Positive	103 ± 2.83 69.89 ± 56.83	0.82	0.416
	EBV				
	IgM	Negative Positive	70.92 ± 55.59 70.40 ± 71.21	0.02	0.984
	IgG	Negative Positive	59.50 ± 44.55 71.23 ± 56.81	0.29	0.774

ALT (U/L)	CMV				
	IgM	Negative Positive	48.40 ± 29.43 40.40 ± 35.21	0.58	0.566
	IgG	Negative Positive	83 ± 19.80 46.72 ± 29.36	1.72	0.089
	EBV				
	IgM	Negative Positive	47.77 ± 29.71 48.20 ± 32.61	0.03	0.976
	IgG	Negative Positive	52 ± 46.67 47.68 ± 29.55	0.20	0.841
Serum calcium (mg/dL)	CMV				
	IgM	Negative Positive	8.76 ± 0.69 8.94 ± 0.36	0.56	0.579
	IgG	Negative Positive	8.65 ± 1.34 8.78 ± 0.66	0.27	0.786
	EBV				
	IgM	Negative Positive	8.79 ± 0.70 8.66 ± 0.29	0.40	0.685
	IgG	Negative Positive	8.60 ± 0.14 8.78 ± 0.68	0.38	0.706
Serum vitamin D (ng/mL)	CMV				
	IgM	Negative Positive	30.72 ± 17.17 55.12 ± 22.07	2.65	0.011
	IgG	Negative Positive	44.35 ± 54.95 32.36 ± 17	0.30	0.809
	EBV				
	IgM	Negative Positive	31.82 ± 18.92 43.85 ± 13.94	1.23	0.224
	IgG	Negative Positive	33 ± 14.10 32.89 ± 18.94	1	0.99
Albumin (g/dL)	CMV				
	IgM	Negative Positive	3.42 ± 0.59 3.16 ± 0.46	0.95	0.344
	IgG	Negative Positive	3.30 ± 1.13 3.40 ± 0.57	0.24	0.810
	EBV				
	IgM	Negative Positive	3.41 ± 0.59 3.24 ± 0.27	0.63	0.530
	IgG	Negative Positive	3.30 ± 1 3.40 ± 0.59	0.24	0.810

4. Discussion

Given the growing prevalence of liver transplantation as a therapeutic option for patients with liver disease, meticulous care for transplant candidates both pre- and post-operation is imperative. Literature reviews suggest that viral infections, such as those caused by CMV and EBV, contribute to reduced post-transplant survival rates. Exploring the impact of these viral infections on the success of liver transplants may enhance both the longevity of the transplant and patient survival. The results indicated that 7.5% of the liver transplant candidates tested positive for CMV IgM and 97% for IgG. Jamalidoust et al. 2021 retrospective study at Namazi Hospital in Shiraz, which sought to quantify CMV load and assess clinical outcomes in liver recipients with reactivated CMV infection, included 657 patients who received transplants from 2014 to 2017. Diagnoses were made using the real-time PCR method. The study found that 151 patients (23%) experienced CMV reactivation at least one-year post-transplant. Of these, 41 individuals (6.2%) died, and 58 (8.8%) faced transplant rejection within the first year following their surgery. Among the deceased, 21 had experienced CMV reactivation. The mortality rate was notably higher in patients with CMV infections compared to those without [27]. Conversely, our study revealed that 97% of patients are at risk of reinfection due to IgG positivity.

In a 2020 retrospective cohort study, the incidence of CMV disease within the first six months post-transplant among liver transplant recipients in Mexico City was examined. Out of 124 patients, four (3.2%) contracted CMV, 96 (85%) exhibited detectable DNAemia, and 25 (22%) remained asymptomatic. The study concluded that the incidence of CMV disease was 3.2% [28], a relatively minor proportion compared to the IgG-positive individuals in our study who may be susceptible to future CMV infections. Moreover, in 2017, Varghese et al. investigated CMV seropositivity in liver transplant recipients. The pre-transplant analysis focused on CMV-related IgG and IgM. Overall, CMV exposure in recipients was found to be 71.8%. Among donors, CMV seropositivity was observed in 90.9% (100 out of 110). Notably, three deaths occurred in recipients who were also positive for CMV via quantitative RT-PCR. The findings of the study indicate a high rate of CMV exposure among both transplant recipients and donors, with the greatest risk associated with recipient reactivation rates. However, the mortality rate due to CMV reactivation was low [29].

In 2013, Dehghani et al. assessed the prevalence of CMV serology in pediatric liver transplant candidates at Namazi Hospital in Shiraz. This descriptive, cross-sectional, and retrospective study analyzed serology data from 98 liver transplant candidates under 18 years old, who were referred to Namazi Hospital between 2006 and 2009. Serological testing for IgM and CMV IgG was conducted using the ELISA method. The research revealed that 92.9% of the pediatric candidates tested positive for IgM and 17.3% for CMV IgG, while 7.1% and 82.7% tested negative for IgM and CMV IgG, respectively, indicating a higher exposure rate compared to our study's subjects [30].

All volunteers and donors must undergo CMV-IgG serology testing prior to transplantation. Recipients lacking CMV antibodies face the highest risk of infection when receiving organs from antibody-positive donors, with rates up to 88% in the absence of prophylaxis. Conversely, the risk is lowest for recipients with negative antibodies receiving organs from similarly negative donors [31]. In light of these findings, Shahinian et al. recommend the use of appropriate prophylactic medications, cytomegalovirus vaccination, and vigilant patient monitoring for viral infections to mitigate CMV infection risks in transplant recipients [26]. Gane et al. conducted a study to evaluate the safety and efficacy of oral ganciclovir in preventing CMV disease following liver transplantation. In this research, 304 liver transplant recipients were randomized to receive either oral ganciclovir at a dosage of 1000 mg or a matching placebo, administered three times daily. The medication was continued until the 98th day post-transplantation, provided the patient could tolerate oral intake. In the initial six months following surgery, patients underwent regular monitoring for indications of CMV infection, CMV disease, graft rejection, opportunistic infections, and potential drug toxicity. The study's findings revealed that the six-month incidence of CMV disease, was 18.9% in the placebo group of 154 patients, compared to 4.8% in the ganciclovir group of 150 patients ($p < 0.001$). Among the high-risk seronegative recipients (R-) receiving seropositive livers (D+), the incidence of CMV disease was 44% out of 25 in the placebo group, versus 14.8% out of 21 in the ganciclovir group ($p = 0.02$). A significant reduction in CMV disease incidence was observed in antibody recipients, with 32.9% out of 37 in the placebo group and 4.6% out of 44 in the ganciclovir group ($p = 0.002$). Oral ganciclovir also decreased the incidence of CMV infection and symptomatic herpes simplex infections. Overall, the researchers concluded that oral ganciclovir is a safe and effective prophylactic for CMV disease post-liver transplantation [32]. It is important to note that serological methods for diagnosing CMV infection can lead to delays that impact patient follow-up. Prompt and timely diagnosis of CMV, which serological tests, such as ELISA cannot provide, is crucial for transplant patient management. In such instances, antigen testing may facilitate the timely detection of the virus.

The study results revealed that five (7.5%) of liver transplant candidates tested positive for EBV IgM and 65 (97%) for IgG. In a study in London, which included 96 pediatric liver transplant patients, the incidence of EBV was found to be 60.4% [33], a notably high rate. Varghese et al., in 2017, examined the seropositivity of the Epstein-Barr viral capsid antigen (EBVCA) in liver transplant donors. Analysis of pre-transplant data from 153 recipients showed that 61.4% [29] had antibodies against EBVCA, mirroring the high rates observed in our study. Halliday et al. 2014 retrospective study assessed the prevalence of EBV in the blood and clinical outcomes of 98 liver transplant recipients. Monitoring EBV DNA levels via whole blood PCR correlated with clinical parameters over a median period of 249 days, revealing that 67% of patients had the EBV blood virus [34], indicating a substantial prevalence of EBV infection among liver transplant patients.

The results of our study indicated that the average serum level of vitamin D in CMV IgM-negative individuals was 30.72± 17.17, while it was 55.12± 22.07 in CMV IgM-positive individuals. For CMV IgG, the average serum levels were 44.35± 54.94 in negatives and 32.36± 17 in positives. Notably, a significant difference was observed in the mean serum level of vitamin D in CMV IgM infections ($p=0.011$), with higher levels in CMV IgM-positive patients. Generally, research suggests that vitamin D does not significantly impede CMV proliferation in vitro. Instead, CMV replication swiftly downregulates the expression of the vitamin D receptor gene, a phenomenon specifically associated with CMV and not typically seen in other viral infections, including EBV. Disruptions in vitamin D homeostasis may influence over 80 pathways linked to cancer, autoimmune diseases, and cardiovascular conditions, potentially predisposing CMV patients to a range of disorders [35]. Beanrde et al. study identified a correlation between lower calcitriol levels and heightened perinatal and early postnatal CMV transmission. However, it remains unclear whether CMV and/or HIV infections diminish vitamin D levels due to the body's increased utilization in combating these infections, or if low maternal vitamin D contributes to a higher susceptibility to viral infections [36].

The findings of this study indicate no significant differences in CMV and EBV infection rates when considering gender, liver enzymes, serum calcium, and serum albumin levels. Our research highlights that the correlation between background variables and CMV/EBV infections yields inconsistent results across various studies. Shirafkan et al. (2016) explored demographic factors and risk factors influencing the onset of cytomegalovirus (CMV) infection post-kidney transplantation. Their findings showed no correlation between the onset of CMV infection and variables such as gender, residence, marital status, education level, BMI, smoking status, hepatitis B, or dialysis type. The only variable associated with the onset of CMV

infection was the patient's age, with older patients being more susceptible to CMV infection post-transplantation. Consequently, it is advisable to conduct more frequent follow-ups during the first four months post-transplantation, particularly within the initial two months [37]. Halliday et al. assessed the prevalence of the EBV blood virus and its clinical outcomes in 98 liver transplant recipients through a retrospective study, noting a prolonged infection duration in male patients [34]. This study has limitations, notably its focus on a patient group in Rasht city, which may not reflect the broader Iranian population. Therefore, future research with larger sample sizes across different cities and provinces is recommended. Further similar research is also encouraged to examine the role of vitamin D in preventing CMV infection in liver transplant recipients more closely.

Our study's results demonstrate a 7.5% prevalence of CMV and EBV infections among liver transplant patients. These findings underscore the necessity of a sustained and targeted program to avert infection-related complications through prompt diagnosis and treatment, which are crucial for favorable outcomes in liver transplant patients.

Authors' contributions

Study design, methodology and supervision: HN, MY, PS. Data collection and analysis: RS, MB. Write a draft and critical revision: RS, HN, MY, MB, PS. All authors read and approved the final version of manuscript.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

The Research Ethics Committee of Guilan University of Medical Sciences approved all processes of the current study (IR.GUMS.REC.1401.310). Informed consent obtained from all of the participants by signing a form in a written format.

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