Research in Molecular Medicine

Difference in the Cytomegalovirus-related Clinical Laboratory Findings Between Patients With Bone Marrow and Kidney Transplantations

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ABSTRACT

Background: Despite close monitoring of transplant patients, Cytomegalovirus (CMV) infection has remained one of the most critical problems in transplantation. This study investigates the relationship between CMV viral load and clinical laboratory findings in transplant recipients.

Materials and Methods: A total of 34 transplant recipients comprising 15 Kidney Transplant (KT) recipients and 19 Bone Marrow Transplant (BMT) recipients admitted to the Imam Reza Hospital in Kermanshah Province, Iran, were enrolled in this study. The CMV viral load was quantified by the real-time PCR technique.

Results: The CMV viral load in KT recipients was significantly higher than in BMT recipients (P=0.03), and there was a positive association between the level of virus and the level of cyclosporine in the blood of patients (r=0.51, P=0.02). Besides, CMV viral load was positively correlated with WBC (r=0.32, P=0.04), urea (r=0.47, P=0.002), creatinine (r=0.39, P=0.01), aspartate aminotransferase (r=0.33, P=0.04), and lactate dehydrogenase (r=0.4, P=0.01). Also, it was negatively associated with albumin (r=-0.61, P<0.001), sodium (r=-0.4, P=0.01), and calcium levels (r=-0.46, P=0.003). There were also significant differences between KT and BMT recipients regarding the CMV-related clinical laboratory findings of urea (P=0.02), creatinine (P=0.001), uric acid (P=0.005), direct bilirubin (P=0.04), albumin (P=0.04), platelet (P<0.001), and sodium (P=0.04) levels.

Conclusion: Based on present data, we conclude that despite careful monitoring of patients, infection with CMV is still one of the most important problems associated with organ transplantation, which is directly related to many laboratory findings.

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Introduction

Cytomegalovirus (CMV) is a large double-stranded DNA (dsDNA) virus belonging to the β-herpesvirus subfamily [1]. CMV is one of the most important infectious agents affecting recipients after transplantation, associated with decreased survival [2]. Transplanted patients have an immune system disorder even several months after transplantation because of taking immunosuppressive drugs. The immune system dysfunction, as well as other epidemiological risk factors that transplant patients are exposed to, makes them highly susceptible to CMV infection [3]. Early CMV diagnosis in patients undergoing transplantation plays a crucial role in the preemptive treatment and can lead to better disease management [3]. Nowadays, patients are closely monitored for CMV infection after transplantation, and CMV viral load measurement is a good predictor of the chance of developing CMV disease [4]. The assessment of the CMV infection in these patients is performed with two assays: the pp65 antigenemia test and the CMV DNA Polymerase Chain Reaction (PCR), which is the preferred test because it is more sensitive than the former assay [5]. Despite close monitoring of patients, CMV infection has remained one of the significant problems in transplantation [6]. Studies show that higher CMV viral loads are correlated with CMV-related complications and clinical symptoms of transplantation [7]. Besides, the reduction in CMV viral load after antiviral treatment is associated with a reduced risk of morbidity and improvement of patients' condition [8]. Several studies are investigating the role of CMV in transplantation outcomes [9]; however, the virus can affect many clinical functions and markers in the body, and to date, few studies have been conducted to identify the exact association between CMV viral load and CMV-related clinical laboratory characteristics.

Therefore, this study aims to determine which laboratory tests are associated with the CMV viral load and whether the CMV-related clinical laboratory findings differ between individuals with bone marrow and kidney transplantations.

Materials and Methods

Study patients

This study investigated the transplant recipients admitted to the Imam Reza Hospital in Kermanshah Province, Iran, between August to November 2019. After excluding ineligible patients because of differences in immunosuppressive drug and conditioning regiment, 34 transplant recipients comprising 15 Kidney Transplant (KT) and 19 Bone-Marrow Transplant (BMT) recipients, who received similar immunosuppressive and antiviral drug protocols, were included in this study. Patients were also checked to see if they had other infections. The type of transplant was allogeneic in 89.47% of BMT patients. All transplant patients were treated with a similar protocol and only in the mentioned hospital. Also, all methods used to mobilize the bone marrow were similar for all BMT patients. At the time of blood sampling of KT patients, no signs of acute rejection, heart failure, and delayed graft function were reported. Table 1 presents the demographic and clinical characteristics of the patients.

Blood sample collection

About 10 mL of fresh venous blood was collected in anticoagulant-containing tubes from all patients (timeline: day 21 post-transplant). By centrifugation of blood samples at 4000 rpm for 5 min, the serum samples were separated and kept at -70°C until further use.

Biochemical measurements

Serum levels of all biochemical parameters, including Fasting Blood Sugar (FBS), urea, creatinine, uric acid, cholesterol, Triglyceride (TG), High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), Aspartate aminotransferase (AST), Alanine transaminase (ALT), Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), bilirubin, albumin, Na, K, Mg, and Ca, were measured by turbidimetry method via commercially available kits purchased from BioSystems Company (Germany) according to their manufacturer's instructions. Finally, the results were read using a Mindray BS-800M analyzer system.

Hematological tests

Also, all hematological experiments were performed by the Mindray BC-6800 analyzer system.

Measurement of CMV viral load

Quantification of CMV DNA in serum samples was performed by the real-time PCR technique (LightCycler 96® instrument, Roche Applied Science, Penzberg, Germany) through a CMV RQ kit (Novin Gene, Iran) based on the manufacturer's instruction. According to the kit instruction, it has a limit of detection equal to 1 copy/µL.

Table 1. Characteristics of the study patients (N=34)

Variables		Values/No.(%)
Type of transplantation	KT	15(44.11)
	BMT	19(55.88)
Sex, Male/Female	Total	22/12(64.7/35.3)
	KT	10/5(66.66/33.34)
	BMT	12/7(63.15/36.85)
Recipient age (y), Mean±SEM	Total	44.63±0.32
	KT	41.0±0.84
	BMT	47.84±0.64
Transplant type (BMT)	Allogeneic	17(89.47)
	Autologous	2(10.52)
Underlying diseases (BMT)	AML	11(57.89)
	ALL	4(21.05)
	Multiple myelomas	2(10.52)
	Anemia	2(10.52)
Underlying diseases (KT)	Renal failure	13(86.66)
	Pancreatitis	1(6.66)
	GI Bleed	1(6.66)
Immunosuppressive regimens	Tacrolimus	26(76.47)
	Cyclosporine	27(79.41)
	Cyclophosphamide	18(52.94)
	Mycophenolate mofetil	4(11.76)
	Thymoglobulin	2(5.88)
	Steroids (Maintenance)	34(100)
Antiviral regimens	Acyclovir	26(76.47)
	Ganciclovir	25(73.52)
	Valganciclovir	21(61.76)
Symptoms	Nausea	10(26.31)
	Vomiting	8(21.05)
	Fever	16(42.10)
	Sepsis	10(26.31)
	Pneumonia	5(13.15)
	Death	7(18.42)

BMT: Bone Marrow Transplantation; KT: Kdney Transplantation; AML: Acute Myeloid Leukemia; ALL: Acute Lymphocytic Leukemia; GI bleed: Gastrointestinal bleeding

Measuring blood cyclosporine level

The level of cyclosporine (at time 0: before taking the morning dose) in whole blood samples was measured by the electrochemiluminescence immunoassay (ECLIA; Cobas e411, Roche Inc., CA, USA) method through a commercial kit (Roche, USA) following the manufacturer's guidelines.

Ethical considerations

This study observed the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Kermanshah University of Medical Sciences (IR.KUMS.REC.1398.848). Before participation in the study, an informed consent form was obtained from all patients. All patients' information was kept confidential. No other process was conducted on the patients.

Statistical analysis

All statistical analyses, calculations, and graph drawings were performed using SPSS software version 23 (SPSS, Chicago, IL, USA) and GraphPad Prism version 8 (GraphPad, Software, La Jolla, California, USA). At first, the data normality was determined by the 1-sample Kolmogorov-Smirnov test. Afterward, the independent sample t test was used to analyze parametric data, and the Mann-Whitney and Kruskal Wallis tests were used to analyze non-parametric data. The Spearman rank-order correlation coefficient analysis was also applied to assess the correlations between study variables. P values less than 0.05 were considered to be statistically significant.

Results

CMV viral load measurement in study patients

A total of 34 patients, 19 with BMT and 15 with KT, were included in the study. Clinical findings are presented in Table 2, which categorizes the patients' characteristics according to the type of transplantation. Interestingly, after blood serum analysis, we found that the CMV viral load was significantly higher in patients with KT than in the BMT group (P=0.03) (Figure 1A). However, no significant differences were observed in our subgroup analyses according to BMT patients (Acute Myeloid Leukemia [AML], Acute Lymphocytic Leukemia [ALL], Multiple Myeloma [MM], and anemia) (Figure 1B).

Clinical laboratory analysis in patients with BMT and KT

We examined whether the clinical laboratory values differed amongst patients with BMT and KT. Blood serum analysis revealed that patients with KT had a significantly higher level of White Blood Cells (WBCs) (P=0.04), platelet (P<0.001), urea (P=0.02), creatinine (P=0.001), uric acid (P=0.005), and AST (P=0.05). In addition, the BMT group showed a significantly higher level of direct bilirubin (P=0.04), albumin (P=0.04), and sodium (P=0.04) (Figure 2).

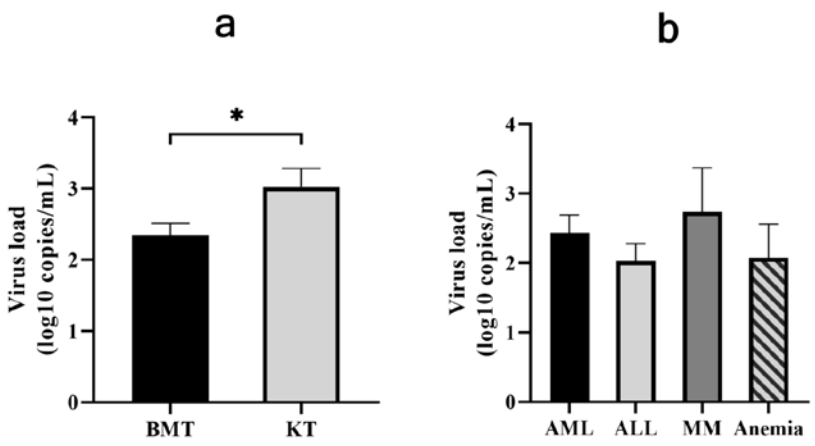

Figure 1. CMV viral load in patients

A: BMT and KT, and B: subgroup analyses according to BMT patients (AML, ALL, MM, and Anemia)

*P-value<0.05.

CMV: Cytomegalovirus; BMT: Bone Marrow Transplantation; KT: Kidney Transplantation; AML: Acute Myeloid Leukemia; ALL: Acute Lymphocytic Leukemia; MM: Multiple Myeloma

Table 2. Laboratory findings of the studied participants

Factors (Unit)	Mean±SD Participants		P
	BMT (n=19)	KT (n=15)	
CMV load (Copies/mL)	1385.74	29226.89	0.03*
WBC (10^3/µL)	5.14±1.62	7.74±2.09	0.048*
RBC (10^6/µL)	3.24±0.12	3.53±0.21	0.47
HB (g/dL)	9.67±0.42	9.89±0.60	0.97
HCT (%)	29.06±1.21	27.60±1.99	0.60
PLT (10^3/µL)	63.26±18.64	152.20±18.38	0.0001***
ESR (mm/h)	7.54±28.21	58.66±16.23	0.24
PT (s)	13.08±0.18	13.12±0.29	0.73
INR (s)	1.06±0.023	1.07±0.04	0.68
PTT (s)	29.05±0.93	30.46±1.60	0.63
FBS (mg/dL)	109.52±6.32	124.00±11.00	0.47
Urea (mg/dL)	44.10±8.33	89.33±20.87	0.02*
Creatinine (mg/dL)	1.10±0.17	3.26±0.79	0.001***
Uric acid (mg/dL)	4.10±0.61	7.22±0.84	0.005**
Cholesterol (mg/dL)	118.25±10.98	122.50±12.50	0.83
TG (mg/dL)	174.93±27.16	305.00±79.00	0.15
HDL (mg/dL)	60.33±8.20	56.0	1.00
LDL (mg/dL)	31.50±8.62	55.0	0.64
AST (U/L)	22.26±4.61	29.93±6.14	0.05*
ALT (U/L)	28.78±7.22	26.00±3.70	0.47
LDH (U/L)	479.36±51.96	611.91±50.27	0.07
ALP (U/L)	227.27±25.66	245.80±34.13	0.70
Bil total (mg/dL)	2.17±1.18	0.67±0.07	0.18
Bil direct (mg/dL)	1.37±0.92	0.27±0.04	0.042*
Alb (g/dL)	4.09±0.16	3.34±0.14	0.043*
Na (mmol/L)	140.05±0.75	136.00±1.37	0.044*
K (mmol/L)	3.81±0.18	4.08±0.16	0.35
Mg (mg/dL)	2.04±0.093	2.06±0.11	0.86
Ca (mg/dL)	9.26±0.20	8.46±0.38	0.12

Values are expressed as Mean±SEM, *P<0.05, **P<0.01, ***P<0.001.

CMV: Cytomegalovirus; BMT: Bone Marrow Transplantation; KT: Kidney Transplantation; WBC: White Blood Cell; RBC: Red Blood Cell; LDH: Lactate Dehydrogenase; AST: Aspartate aminotransferase; HDL: High-density Lipoprotein; Na: Sodium; HB: Hemoglobin; HCT: Hematocrit; PLT: Platelet; ESR: Erythrocyte Sedimentation Rate; PT: Prothrombin Time; INR: International Normalized Ratio; PTT: Partial Thromboplastin Time; FBS: Fasting Blood Sugar; TG: Triglyceride; LDL: Low-density Lipoprotein; ALT: Alanine aminotransferase; ALP: Alkaline Phosphatase; Bili: Bilirubin; Alb: Albumin; K: Potassium; Mg: Magnesium; Ca: Calcium.

Correlation between pooled CMV viral load and clinical laboratory values

The independent effects of CMV on transplantation associated laboratory values in all subjects were assessed by the Spearman rank-order correlation coefficient analysis (Figure 3). As expected, pooled CMV viral load was positively correlated with cyclosporine levels (r=0.51, P=0.02). However, subgroup correlation between CMV viral load and cyclosporine levels based on BMT patients (AML, ALL, MM, and anemia) were not statistically significant (rAML =0.41, P=0.26; rALL =0.5, P=0.66). Our data also showed that pooled CMV viral load was positively correlated with WBC (r=0.32, P=0.04), urea (r=0.47, P=0.002), creatinine (r=0.39, P=0.01), AST (r=0.33, P=0.04), and LDH (r=0.4, P=0.01). Besides, CMV viral load was negatively correlated with albumin (r=-0.61, P<0.001), sodium (r=-0.4, P=0.01), and calcium (r=-0.46, P=0.003). CMV viral load was not correlated with other laboratory values (P>0.05).

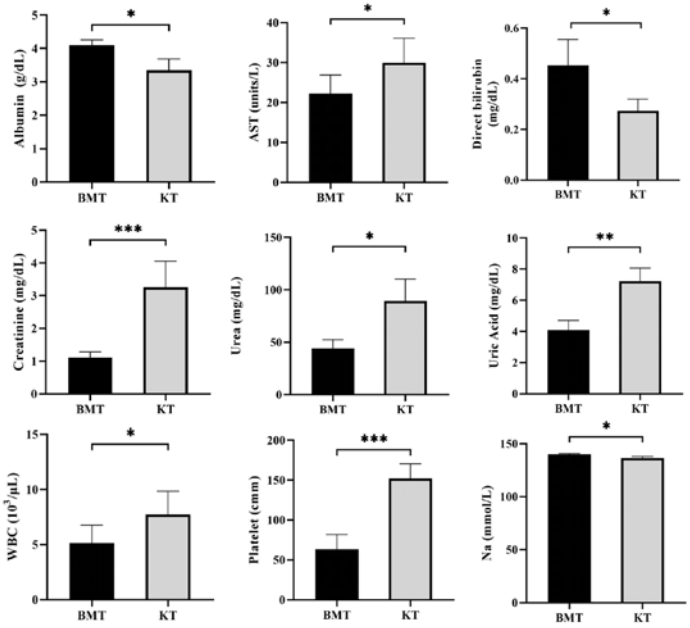

Figure 2. Clinical laboratory analysis in patients with BMT and KT

* P<0.05, ** P<0.01, *** P<0.001.

BMT: Bone Marrow Transplantation; KT: Kidney Transplantation; WBC: White Blood Cell; AST: Aspartate aminotransferase; Na: Sodium

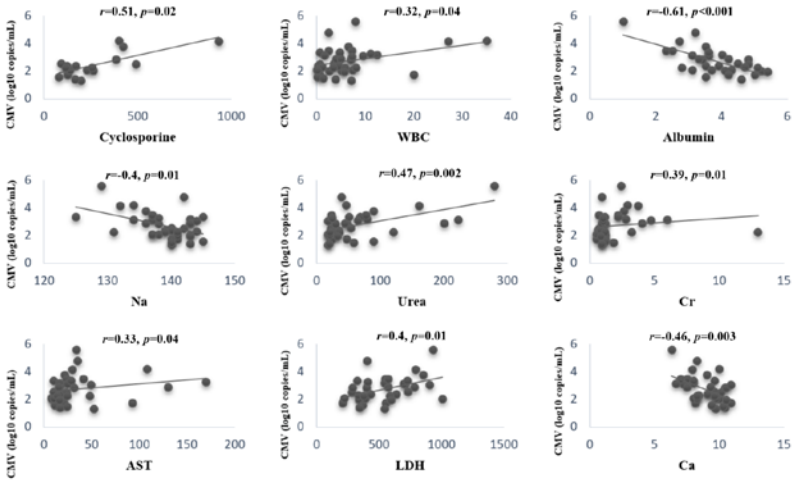

Figure 3. Total correlation between CMV viral load and clinical laboratory values in both BMT and KT groups

CMV: Cytomegalovirus; BMT: Bone Marrow Transplantation; KT: Kidney Transplantation; WBC: White Blood Cell; LDH: Lactate Dehydrogenase; AST: Aspartate aminotransferase; Cr: Creatinine; Ca: Calcium; Na: sodium.

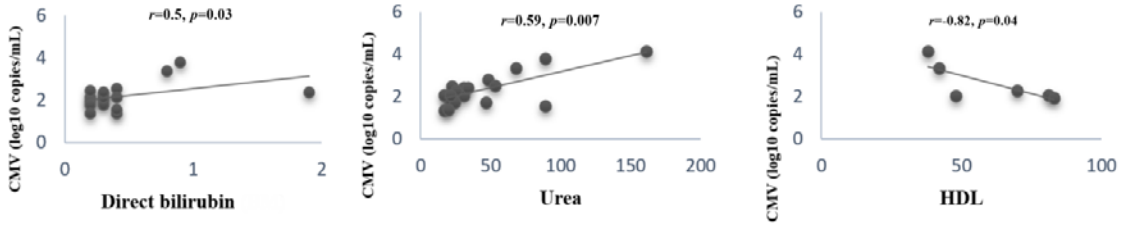

Figure 4. Correlation between CMV viral load and clinical laboratory values in patients with BMT

CMV: Cytomegalovirus; BMT: Bone Marrow Transplantation; HDL: High-Density Lipoprotein.

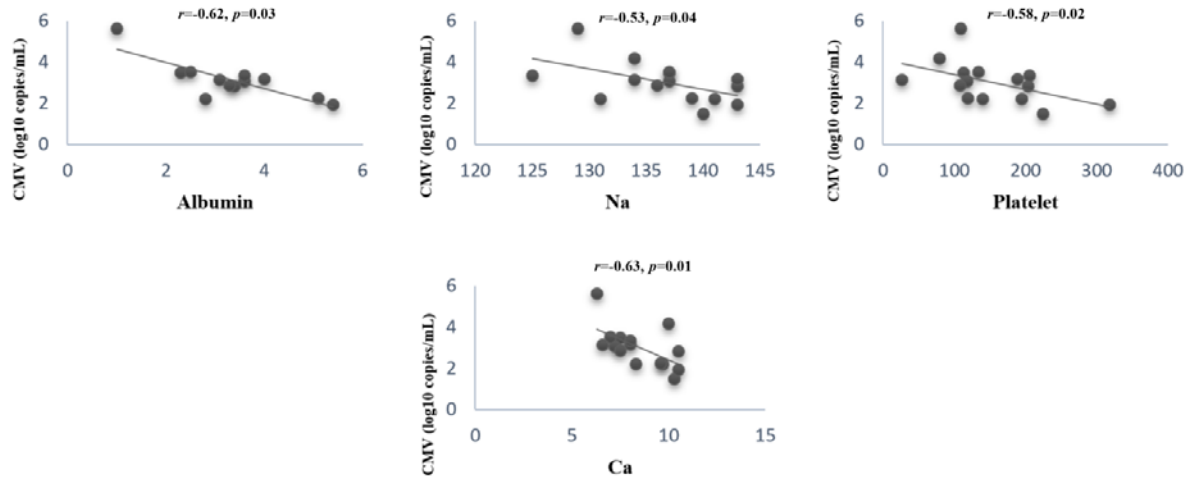

Figure 5. Correlation between CMV viral load and clinical laboratory values in patients with KT
CMV: cytomegalovirus; KT: kidney transplantation; Na: sodium; Ca: calcium.

The difference in CMV-related clinical laboratory values between BMT and KT groups

In both BMT and KT groups, all laboratory values were examined for correlation with CMV viral load with the Spearman rank-order correlation coefficient analysis (significant correlations were shown in Figure 4 and Figure 5, respectively). In the BMT group, our data showed that CMV viral load was positively correlated with direct bilirubin (r=0.5, P=0.03) and urea (r=0.59, P=0.007), and negatively correlated with HDL (r= -0.82, P=0.04). Contrary to what is observed in the BMT group, in the KT group, CMV viral load was negatively correlated with albumin (r=-0.62, P=0.03), platelet (r= -0.58, P=0.02), sodium (r=-0.53, P=0.04), and calcium (r=-0.63, P=0.01). Due to a negative correlation with platelet, there was also a positive correlation between CMV viral load and prothrombin time (r=0.6, P=0.01).

Discussion

CMV infection is a significant problem in BMT recipients, and regardless of the prior viral load status of patients, 32%-70% of cases are in danger of CMV infection [10], especially after allogeneic BMT and the first 3-4 months after transplantation [11]. Moreover, the incidence of CMV infection is between 8% and 32% after KT and occurs mainly between 30 and 90 days after transplantation [12]. The present study showed that the CMV viral load in kidney transplant patients was higher than in bone marrow transplant patients, while both groups of patients had taken similar antiviral drugs in close doses. Studies showed that approximately 30% of patients undergoing allogeneic transplantation develop CMV disease. In BMT, reactivation usually occurs within the first 30 days after transplantation and in those who develop Graft Versus Host Disease (GVHD). The incidence of CMV is also between 20% and 32% after kidney transplantation. In KT, the greatest CMV viral load can be due to a serological mismatch between the donor and the recipient and a less intensive conditioning regimen. In addition, the difference in CMV viral load observed in our experiments may be due to differences in the reactivation of CMV in BMT and KT so that that virus might be activated in the latent stage in BMT, and our tests failed to detect it early. Besides, there was a positive association between the level of virus and the level of cyclosporine in the blood of transplanted patients indicating that patients with higher cyclosporine levels are more likely to be infected with the CMV. Our results were in line with the results of other studies, including the Sakhuja et al. study on Indian renal transplant recipients. They showed a significant increase in the incidence of CMV infection in patients after introducing cyclosporine [13]. Moreover, studies on cardiac transplant recipients, including a recent study in 2018 by Marina M.K. Bond et al. [14] and a randomized Spanish study in 2014 [15] reported the same results.

Different studies showed that WBCs are the most common site of the active CMV genome during viremia [16]. Some studies on solid organ transplantation, such as kidney and heart transplantation, indicated that leucopenia was associated with CMV disease [17-19]. However, the results of our study show that WBCs were higher in KT patients, who had higher levels of CMV than those in the BMT group. Also, contrary to the studies mentioned above, our results showed a positive relationship between

the CMV viral load and blood leukocyte levels. The decrease in blood leukocytes reported in some studies can be due to drugs used by transplanted patients, including antiviral and immunosuppressive drugs. Moreso et al. [18], after a study on kidney transplant recipients, reported that patients who received high doses of Mycophenolate Mofetil (MMF) and conventional treatments of cyclosporine showed leucopenia during CMV infection.

In contrast, in other patients who received similar doses of MMF but lower doses of cyclosporine, leucopenia has not been reported [18]. Besides, Ainger et al. reported that 36.8% of lung transplant recipients developed leucopenia after treatment with Vlganciclovir (VGC) [20]. Taber et al. also reported that the overall incidence of leucopenia was 11% after VGC therapy in transplant recipients [21]. Moreover, I-Ming Chen et al. reported that severe leucopenia might occur in the first month after VGC therapy in Chinese cardiac transplant recipients [22]. However, Margaret E. Cooke et al.'s study on heart transplant recipients indicates that CMV activation is closely associated with the reduction in the total WBC count, but there is no association between the decrease in leukocyte count and immunosuppressive therapy [17].

Shunya Kaneshita et al.'s study on patients with rheumatic disease and J.M. Kim et al.'s study on liver transplant recipients report that hypoalbuminemia can be a possible risk factor for CMV disease [23, 24]. Gautam Borthakur et al.'s study on patients with chronic lymphoproliferative diseases and Jianhua Hu et al.'s study on patients with Acute-on-Chronic Liver Failure (ACLF) also show the same results [25, 26]. Besides, S.W. Yang et al.'s study conducted on 375 renal transplant recipients indicates that a lower albumin level is associated with poor long-term graft outcomes and more post-transplantation complications such as CMV infection [27]. The results of our study were in line with the results of the above studies and showed a significant negative correlation between the CMV viral load and serum albumin level. Also, kidney transplant recipients with a higher level of CMV had a lower level of serum albumin than the BMT group.

Many patients with Hematopoietic Cell Transplantation (HCT) experience liver injury and elevated serum bilirubin, associated with increased mortality following HCT [28]. Besides, the elevation of liver transaminase levels is a common feature of acute CMV infection, occurring in up to 92% of patients [29]. Veronique Erard et al. showed that the high bilirubin level was associated with elevated mortality risk after HCT [30]. Moreover, Ted A. Gooley et al. conducted a cohort study on 1419 patients with myeloablative allogeneic HCT and reported that an increase in bilirubin from 1 to 3 mg/dL was correlated with an elevated risk of mortality [28]. Besides, Miyajima et al. studied 44 children who underwent BMT and reported that the abnormal liver function tests occurred more frequently in patients with CMV infection (63.4%) than in patients without CMV infection (16.0%) [31]. Our study results also showed that levels of AST and LDH in the KT group were higher than those in the BMT group, and there was a significant positive correlation between the level of these enzymes and the level of CMV. On the other hand, the level of direct bilirubin was higher in the BMT group, and there was a significant positive correlation between the CMV viral load and the direct bilirubin level, which is in line with the results of the studies mentioned.

Recent studies have shown that CMV reactivation was associated with increased urea and creatinine levels, and there was a positive correlation between CMV viral load and urea levels [32]. Besides, studies on KT recipients who developed CMV disease report an elevated creatinine level in these patients. A cohort study on 87 KT recipients reported that 55 showed CMV infection, and a high creatinine level was a significant symptom in patients (14.5%) [33]. Moreover, Maarten H.M. Raasveld et al.'s study on 86 KT recipients and F. Pour-Reza-Gholi et al.'s study on 100 KT recipients also show that serum creatinine increases in patients who develop CMV disease [34, 35]. As expected, the results of our study also show that levels of urea and creatinine are significantly higher in the KT group than that in the BMT group, and there is a significant positive correlation between CMV viral load and urea and creatinine levels, especially in the BMT group.

Thrombocytopenia has been reported in immunocompromised patients with CMV infection, but it has only been rarely reported in immunocompetent individuals [36-38]. During active disease, CMV is released into the blood, allowing CMV–platelet interactions [39]. Our results show that platelet count in KT patients is significantly lower than in BMT patients, but this difference may also be due to underlying disease. Interestingly, there is also a significant negative relationship between CMV viral load and platelet count in the KT group, increasing prothrombin time in patients with lower platelet count.

Our study indicates that the CMV viral load in KT recipients is higher than that in BMT recipients, and there is a positive association between the level of virus and the level of cyclosporine in the blood of patients. Interestingly, our results, in contrast to similar studies, show a positive relationship between the CMV viral load and blood leukocyte levels. There was also a difference in the

CMV-related clinical laboratory findings between KT and BMT recipients, indicating that the CMV function may differ in some conditions.

Conclusion

In conclusion, despite careful monitoring of patients, infection with CMV is still one of the most important problems associated with organ transplantation and is directly associated with many laboratory findings. Whether in transplant patients or healthy individuals, who have CMV infection, many laboratory characteristics are affected by the virus. This outcome should be considered in clinical decision-making because kidney, liver, and hematological problems, which are initially diagnosed, maybe due to the virus, and they can be alleviated by taking antiviral treatments. Besides, in the different types of transplantation, laboratory findings associated with CMV do not change uniformly, and this issue should be noted in monitoring transplant recipients. However, the present study had some limitations. First, the small size of the sample and the lack of a control group (healthy individuals to compare the status of infection with CMV) may lead to biases in the final conclusion. Second, in the pooled analysis (total transplant patients), it cannot be claimed that 'apples' are compared with 'apples,' and there are certainly differences in the cellular nature of bone marrow transplantation and the tissue nature of kidney transplantation. Thus, further studies with larger samples on other organ transplants are needed to gain a comprehensive view of the function of the CMV in transplanted patients.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Kermanshah University of Medical Sciences (Code: IR.KUMS.REC.1398.848).

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Authors' contributions

All authors have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declared no conflict of interest.

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