Prevalence and Recurrence Rates of Cytomegalovirus Infection among Patients with Hematological Diseases of the Brazilian Western Amazon

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Research Article

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Abstract

Purpose: Cytomegalovirus (CMV) is a worldwide distributed pathogen that may cause serious complications in patients with hematological diseases. This study aimed to serologically characterize the CMV infection in patients suffering from hematological diseases in Amazonas, Brazil. Methods: Serum samples from 323 patients were tested for the presence of anti-CMV IgM or IgG antibodies by an enzyme-linked immunosorbent assay. Positive samples for IgM were submitted to the IgG avidity test to differentiate primary infection from recurrent infection. An epidemiological questionnaire was administered to collect sociodemographic information of the study population. Results: The overall prevalence of CMV infection verified in this study was 91.3%. The highest rates were found in patients suffering from platelet disorders (94.5%), anemia (93.3%), or leukemia (91%). The study population was predominantly composed of individuals with low socioeconomic status. Blood transfusions were more often in patients with anemia or leukemia, but it was not correlated with the positivity for CMV infection. Measurement of IgG avidity in patients positive for anti-CMV IgM demonstrated a recurrent infection rate of 5.2% (17/323). Over 80% of recurrent infection occurred in patients with acute lymphocytic leukemia (ALL) or anemia. Conclusions: Our findings indicated that CMV infection is highly prevalent in patients with hematological diseases from the Brazilian western Amazon. The prevalence observed progressively rose with increasing age, whereas anemia or ALL disease figured as risk factors for the recurrence of CMV infection.

Introduction

Cytomegalovirus (CMV) is a human herpesvirus endemic throughout the world [1]. Viral transmission occurs via intimate contact with infected bodily fluids and through transplacental transfer, blood transfusion, or organ transplantation [2,3].

Primary infection is usually asymptomatic in immunocompetent individuals. However, nearly 10% of infected individuals show symptoms characterized especially by the self-limiting mononucleosis-like syndrome [4,5]. In patients suffering from immunodeficiency or hematological disorders, CMV infection can cause substantial morbidity and mortality due to the virus dissemination to multiple organs as a result of uncontrolled viral replication [6,7]. In these patients, the possibility of CMV transmission through blood transfusion remains a constant concern.

CMV prevalence varies globally, with the rates reaching 100% in developing countries [8,9]. Prevalence rates of 41.9%, 74.4% and 50.4% have been reported in France, Croatia and the United States, respectively [10–12]. In Brazil, there are few studies regarding the epidemiology of CMV infection. Previous reports have demonstrated different prevalence rates of CMV infection in Santa Catarina (96,4%), Rio de Janeiro (78,7%) and São Paulo (84,8%) [13,14].Increasing CMV prevalence was also associated with kidney transplants in Northern Brazil [1,15].

Although epidemiological studies describing CMV infection in patients with hematological diseases are scarce, elevated prevalence rates were reported in patients with thalassemia (91%) and hematological malignancies (82%) [16,17]. In the state of Bahia, Brazil, patients with different hematological diseases also showed elevated seroprevalence for CMV infection (89.4%) [18]. This infection might produce a broad impact on the prognosis of these patients. Previous reports have indicated the association between CMV infection and the development of hematological disorders [8,9]. For example, cytopenia usually found in patients submitted to hematopoietic stem cell transplant is frequently linked to CMV infection [19].

The studies mentioned above demonstrate the importance of the epidemiological surveillance of CMV infection to the clinical management of patients suffering hematological diseases. Therefore, the aim of the present study was to describe the epidemiological profile of the CMV infection among patients with hematological diseases from the Brazilian western Amazon.

Materials And Methods

Study Population

From December 2016 to August 2017, we randomly recruited 323 patients from attendees at the outpatient clinic of the Hemotherapy and Hematology Hospital Foundation of Amazonas – HEMOAM. Only patients with a confirmed diagnosis for hematological diseases were eligible to participate in this study. A standardized interviewer-administered questionnaire was used to obtain information on sociodemographic and risk factors variables. Individuals of both sex and different ethnicities aged 1 to 92 years were selected. This study was approved by the Human Research Ethics Committee of the Hematology and Hemotherapy Hospital Foundation of Amazonas (approval number: 1.994.410). We ensured confidentiality to all participants, as well as the right to refuse to answer questions that could cause constraints during the study. Patients submitted to anti-viral treatment during the research period were excluded of the study to avoid any confusion bias.

CMV Infection Diagnosis

Serum samples from the study population were tested for CMV IgM and IgG antibodies (Abs) through an enzyme-linked immunosorbent assay, performed according to the manufacturer's information (Serion ELISA classic, SerionGmbH, Germany). The optical density was measured in a spectrophotometer using a 405 nm filter, and the test positivity was determined according to the cut-off formula indicated by the manufacturer. To estimate the cut-off ranges, the mean value of optical densities (OD) of the positive controls was multiplied with the numerical data from the quality control certificate (OD = 0.600 x positive control mean for upper cut-off; OD = 0.350 x positive control mean for lower cut-off).

To differentiate primary infection from recurrent infection, serum samples from patients who were positive for IgM were submitted to the IgG avidity test. For this assay, the same commercial kit and protocol were used. However, one elution step was added with an 8M urea solution as agent antigen

binding of low avidity. The tests were performed in duplicate, and the samples were tested with the addition of 8M urea and without urea. The avidity index was calculated by the ratio of the samples Optical Density (OD) values that were treated with 8M urea by the samples OD values that were untreated with urea, multiplied by 100 (IgG + 8M urea/IgG × 100). Avidity index <45% was considered as indicative of recent infection and >65% as recurrent infection.

Statistical Analysis

Descriptive statistical analysis was used to evaluate the sociodemographic variables by calculating measures of central tendency and dispersion. The results were categorized according to normality. The Odds Ratio (OR) analysis was employed to assess the association between socio-demographic factors and the type of hematological disease with susceptibility to CMV infection. OR values were estimated from log-binomial models. One way ANOVA was used to compare the serum levels of CMV antibodies among the study population. The F-test was applied to evaluate the variances of the serum antibody levels. All statistical analyses were performed using Graphpad Prism v.5.0 and Biostat v.5.0. A value of $p < 0.05$ was considered significant.

Results

Prevalence of CMV Infection According to Hematological Disease and Blood Transfusion Rates

The presence of CMV IgG Abs was detected in 295 patients (91.3%) (Table 1). From this number, 179 underwent 2 or more blood transfusion during a one-year period. However, the association between transfusion and prevalence rates was not statically significant ($p = 0.36$).

The prevalence of CMV infection according to the hematological diseases and blood transfusions rates (one-year period) observed in this study are shown in Figure 1. Leukemia was the most prevalent hematological disease in the study population. Patients with leukemia showed CMV prevalence and blood transfusion rates of 93.3% and 77.77%, respectively. Anemia (different etiologies) was the second most frequent disease (Figure 1). A total of 37 patients (50.68%) was carrier of severe anemia. These patients were often submitted to multiple blood transfusions per year.

Patients with lymphoma and immune thrombocytopenic purpura (ITP) exhibited CMV prevalence of 91.7% and 94%, respectively (Table 2). Individuals with sickle cell anemia had the highest blood transfusion frequency (82.35%) and exhibited a CMV prevalence of 94.11%.

CMV prevalence According to Sociodemographic Characteristics of Study Population

Most of the patients declared themselves as brown (65.3%) and single (70.5%). The average age of the study population was 26 years (Table 3). The prevalence of CMV infection observed among brown and black patients was 92.3% and 91.3%, respectively, whereas in white patients the CMV prevalence was 89.9%. No statistically significant association was observed between seropositivity for CMV infection and ethnicity or marital status.

The study population was comprised of individuals with low education and purchasing power levels. The majority of patients was from families earning a minimum (50.4%) or two to five minimum wages (44.9%). Individuals with middle-level education (26.1%), complete high school (22%), or elementary school (20.7%) were more frequent in the study population. Individuals in the elementary education showed decreased susceptibility to CMV infection (p = 0.0002). The association between CMV infection and occupation of student was also statistically significant (p = 0.005), suggesting also that students are less susceptible to CMV infection. No correlation was observed between condom usage and positivity for CMV infection. An overwhelming number of patients did not know about CMV infection (94%), especially regarding transmission and prevention (Table 3).

CMV Serological Profile of the Study Population

Hemophilic patients presented higher CMV IgG serum levels (OD. Mean = 1.842) when compared to the other groups of patients (Supplementary Figure 1A). Sex-based analysis showed similar prevalence rates (p = 0.750) between women (92.1%) and men (90.5%) (Supplementary figure 1B).However, when the results were stratified according to age, prevalence rates gradually rose with increasing age (Figure 2). Furthermore, our findings demonstrated that patients aged 1–10 or 11–19 years exhibited lower levels of serum CMV IgG (mean OD = 1.494 and 1.562, respectively). In contrast, patients aged 20–29 years old displayed the highest levels (mean OD = 1.774) The difference in serum CMV IgG levels observed between the age groups 1-10 and 20-29 was statistically significant (p = 0.02) (Figure 2).

The occurrence of active CMV infection was assessed trough the detection of serum IgM Ab. A positivity of 5.3% (17/ 323) for CMV IgM Ab (Table 4) was observed among the study population. CMV-IgM positive patients were carriers of anemia of different etiologies (n = 7), ALL (n = 7), lymphoma (n = 2) and thrombocytopenia (n = 1) (Table 3). Patients with anemia presented the higher IgM levels (O.D. mean = 0.763). The CMV IgM Abs serum levels variance verified between patients with anemia and ALL was statistically significant (p = 0.01) (Figure 3 A). No statistical significance was verified between IgM Abs positivity and sex (p = 0.45) (Figure 3 B).

The IgG avidity test revealed that all CMV active infection resulted from a recurrence of the infection, since the individuals showed an avidity index higher than 60% (Figure 4).

Discussion

Despite the CMV infection is widespread all over the world, the epidemiological surveillance of this virus is still neglected [20]. Raising awareness of CMV dissemination in Brazil is imperative to combat the infection and to the clinical management of patients, especially patients with hematological diseases.

Our findings demonstrated that the CMV infection is highly prevalent among patients with hematological diseases from the Brazilian western Amazon. The study population showed a prevalence rate (91%)higher than the one observed (67.6%) in the city of Manaus [21]. Likewise, a study carried out in the Hemotherapy and Hematology Foundation of the State of Bahia (HEMOBA), in Brazil, verified an

increased prevalence rate of CMV infection (89.4%) in patients with different hematological diseases [2]. Preeminent seropositivity for CMV infection were also observed in patients with thalassemia (94.1%) from Iran and patients with idiopathic thrombocytopenic purpura (86.4%) from China [22]. Our results reveal a wide CMV circulation in the study population. The present study is a pioneer in describing the epidemiology of CMV infection in patients suffering from hematological diseases in the Brazilian western Amazon.

CMV infection tends to be more frequent in women than in men. This situation probably happens due to the greater susceptibility of women to sexual transmission and because women generally spend more time taking care of children (working in daycare centers or at home), as suggested by some studies [6,23]. Indeed, the risk of primary CMV infection is increased in women of childbearing age [10,24]. In this study, we did not find any correlation between sexes and susceptibility to CMV infection. Similarly, no difference in prevalence rates was observed in white and non-white individuals, even though the positivity for CMV infection has been found 30% higher in non-white people earlier [23]. Our findings also demonstrated that elementary education and the occupation student was directly associated with the low susceptibility to CMV infection. However, the low level of education, inadequate sanitary conditions, cultural aspects, and families with a great number of individuals were already described as the main factors behind the elevated CVM prevalence rates [12,23,25]. Similarly, previous findings showed CMV prevalence ranging from 75% to 97.7% among university students from Middle West [26,27].Nevertheless, the majority of students of the study population were very young, which may explain the low susceptibility to CMV infection verified in these groups once the prevalence rates were more prominent among older people.

Sexual transmission of CMV may be facilitated by viral persistence in the female genital tract, representing an important way of transmission in sexually active adults and adolescents[28]. In developed countries, CMV infection frequently happens in two moments: during the first 2-3 years of life or between adolescence and adulthood (16 to 30 years)[29]. In the present study, nearly half of the patients (43.7%) declared no condom usage during sexual intercourse, but we did not find any correlation between this factor and the susceptibility for CMV infection.

Our results demonstrated that the prevalence of CMV infection was greater in patients with anemia of different etiologies (93.3%), platelet diseases (94.9%), lymphoma (91.7%), and leukemia (91%). Increased prevalence of CMV infection has been previously described in patients with aplastic anemia, lymphoma, or leukemia [30–32]. In some cases, the development of these diseases and the morbimortality of patients were related to CMV infection [30,32,33]. Epidemiological studies showing CMV infection prevalence in patients with platelet disease are scarce, but the correlation between the development of thrombocytopenia and CMV infection was also reported. Although this is not a typical situation, CMV infection may lead to thrombocytopenia or thrombocytopenic purpura in healthy children during the neonatal period [34]. In the present study, we did not analyze the association between CMV infection and the development of these diseases, nor its connection with the enhancement of patients' morbimortality. However, the epidemiological surveillance of CMV infection in patients with hematological diseases provided by this study may be an important tool to improve their clinical management.

Detection of serum CMV IgM Abs may indicate a recent infection or a recurrent infection (reactivation/reinfection) [35–37]. Elevated IgM and low IgG Abs titers suggest primary infection rather than reactivation or reinfection [38]. All 17 active infections observed in our study resulted from recurrent infection since the patients presented high avidity CMV IgG. Positivity rates for CMV IgM Abs vary according to population, culture and region. A study carried out with women in reproductive age from the United States verified 2.9% of positivity for CMV IgM Abs [38]. Pregnant women from Ireland showed 5.9% of positivity for CMV IgM Abs, whereas among patients undergoing hemodialysis from Croatia the rate observed was 2.3% [39,40]. In Brazil, 1.9% of blood donors from the Southern region showed CMV IgM positivity [13]. The present study found a seropositivity of 5.3% for CMV IgM Abs in the study population, which is higher than most of the rates described elsewhere. These findings suggest that the hematological diseases may influence the recurrence of CMV infection.

In the context of the hematological diseases, recurrent CMV infection has been typically associated with the immunosuppression caused by therapeutic schemes. Patients suffering from chronic lymphocytic leukemia showed a CMV reactivation rate of 66% after alemtuzumab therapy [38]. Furthermore, an elevated proportion of CMV reactivation (84.6%) was observed in children with hemoglobinopathies submitted to hematopoietic stem cell transplantation and alemtuzumab treatment [42]. In the present study, we did not assess the clinical records of the study population to search for possible links between treatment and the recurrence of CMV infection.

Most patients positive for CMV IgM Abs suffered from ALL or anemia (various etiologies). CMV reactivation is considered elevated individuals with Leukemia. Increased rates of CMV reactivation were equally noted in patients with leukemia from India (11.3%) and Iraq (12%) [43,44]. Another study observed CMV reactivation in 66% of patients with chronic lymphocytic leukemia, after alemtuzumab therapy [41]. These studies indicate that leukemia increases the risk of CMV recurrent infection by unknown mechanisms. However, it has been recognized that the Natural Killer (NK) cells are the key factor to combat CMV infection [45]. Indeed, NK cell abnormality or deficiency is a risk factor for CMV reactivation [46]. This condition could explain the occurrence of elevated CMV reactivation among patients with ALL described in this study and elsewhere, once NK cell abnormalities were already reported in these patients [47]. In this study, we did not assess the phenotype of NK cells in patients positive for CMV IgM to verify this correlation. Yet, our findings raise the following questions: Would the patients with ALL or anemia be more prone to CMV recurrence? Are the recurrence rates associated with immunological suppression condition inflicted by ALL or Anemia diseases? A longitudinal study with a larger sample size must be done to answer this question.

In the present study, we assessed the serum levels of CMV IgG Abs according to age. The lowest serum levels were observed among children aged 1–10 years, whereas patients aged 20–29 years showed the highest IgG serum levels. A study conducted in the United States with 6.067 women aged 12–49 years demonstrated that serum levels of both IgM and IgG anti-CMV increased gradually with age progression [38]. This correlation was equally observed in a study carried out with 3.304 individuals from Portugal [48].The presence of high serum levels of anti-CMV IgG antibodies has also been linked to the

progression of HIV disease in patients from Uganda, Africa [49]. Also, the clinical course of CMV infection in patients submitted to kidney transplants was associated with anti-CMV antibody titers [50]. At present, no correlation between serum levels of anti-CMV antibodies and hematologic disease progression has been identified.

Although the present study found no significant difference in anti-CMV Ab serum levels when it was analyzed according to the hematological diseases, these serum levels may be used as an indicator of immunocompetence status in the context of hematologic disease. Also, CMV infection could be a key factor linked to patient morbidity. Thus these findings bring new insights not only regarding the epidemiological profile of CMV infection in the study population but also concerning the influence of the hematological disease on the infection recurrence and vice-versa. Therefore, the data presented here may be a starting point for new studies, especially the ones that try to elucidate the negative prognostic impact of CMV infection in patients with hematological disease.

Declarations

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Code availability: Not applicable

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Ethical approval: This study was approved by the Human Research Ethics Committee of the Hematology and Hemotherapy Hospital Foundation of Amazonas (approval number: 1.994.410).

Informed consent: All the patients include in this study signed a written consent form**.**

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Tables

Table 1. Prevalence of CMV infection in patients with hematological diseases.

CMV IgG	N (%)	Transfusion Rates * (%)	OD (95% CI)	*p*-value
Seropositive	295 (91.3)	179 (60.66%) **	0.8573 (0.3823–1.922)	0.360
Seronegative	28 (8.7)	18 (72%) ***		
Total	323	197 (61%)		

OR = Odds Ratio; CI = Confidence Interval. * number of patients submitted to 2 or more transfusion during a one-year period; ** percentage taking account the total number of seropositive individuals; *** percentage taking account the total number of seronegative individuals.

Table 2. Prevalence rates of CMV infection according to the hematological disease.

Hematological Diseases	N	Positive N (%)	Negative N (%)	OR (95% CI)	*p*-value
Anemia (Aplastic, Sickle cell, Hemolytic and others)	90	84 (93,3)	6 (6,7)	1.45 (0.57–3.72)	0.565
Platelets diseases	39	37 (94,9)	2 (5,1)	1.86 (0.42–8.18)	0.592
Spherocytosis	2	-	2 (100)	-	
Hemophilia	9	9 (100)	-	-	
Hemoglobinopathies	3	3 (100)	-	-	
Leukemia	144	131 (91,0)	13 (9,0)	0.92 (0.42–2.00)	0.994
AML	24	23 (95,8)	1 (4,2)	-	
CML	14	13 (93)	1 (7)	-	
ALL	100	91 (91)	9 (9)	-	
CLL	3	3 (100)	-	-	
ATL	2	2 (100)	-	-	
Lymphoma	24	22 (91,7)	2 (8,3)	1.04 (0.23–4.70)	0.751
Multiple myeloma	4	3 (75)	1(25)	-	
Polycythemia	1	-	1 (100)	-	
Myelodysplastic Syndrome	3	3 (100)	-	-	
Thalassemia	4	3 (75)	1 (25)	-	

ALL = Acute Lymphocytic Leukemia; AML = Acute Myeloid leukemia; CLL = Chronic Lymphocytic Leukemia; CML = Chronic Myeloid Leukemia; ATL = Adult T-cell Leukemia/Lymphoma; OR = Odds Ratio; CI = Confidence Interval.

Table 3. CMV infection prevalence according to sociodemographic characteristics of the study population.

Sociodemographic Characteristics	N (%)	Age range	CMV-positive N (%)	CMV-negative N (%)	OR (95% CI)	*p*-value
Ethnicity						
Black	23 (7.1)	2-53	21 (91.3)	2 (8.7)	1.00	
White	89 (27.6)	1-92	80 (89.9)	9 (10.1)	0.79 (0.34-1.81)	0.728
Brown	211 (65.3)	1-90	194 (91.9)	17 (8.1)	1.24 (0.56-2.75)	0.742
Family income						
1 minimum wage	163 (50.5)	1-90	149 (91.4)	14 (8.6)	1.02 (0.47-2.22)	0.884
2 to 5 minimum wages	145 (44.9)	1-92	132 (91.0)	13 (9.0)	0.93 (0.43-2.03)	0.978
6 to 9 minimum wages	13 (4.0)	7-67	12 (92.3)	1 (7.7)	1.00	
More than 10 minimum wages	2 (0.6)	48-55	2 (100.0)			
Level of schooling						
Illiterate*	23 (7.3)	1-92	22 (95.7)	1 (4.3)	2.13 (0.27-16.50)	0.729
Literate**	29 (9.2)	4-90	27 (93.1)	2 (6.9)	1.27 (0.28-5.72)	0.972
Elementary school	38 (12.1)	6-15	28 (73.7)	10 (26.3)	0.17 (0.07-0.42)	**<0.0001**
Incomplete middle school	7 (2.2)	12-14	6 (85.7)	1 (14.3)	0.54 (0.06-4.71)	0.900
Complete middle school	82 (26.1)	7-78	77 (93.9)	5 (6.1)	1.00	
Incomplete high school	1 (0.3)	16	1 (100.0)			
Complete high school	69 (22.0)	16-77	66 (95.7)	3 (4.3)	2.38 (0.69-8.24)	0.246
Undergraduate	35 (11.1)	19-67	33 (94.3)	2 (5.7)	1.60 (0.36-7.12)	0.766
Not Informed	30 (9.6)	3-90	27 (90.0)	3 (10.0)		
Occupation						
Student	94 (48.2)	5-33	79 (84.0)	15 (16.0)	0.11 (0.03-0.51)	**0.002**
Housewife	41 (21.0)	22-90	39 (95.1)	2 (4.9)	1.00	
Retired	17 (8.7)	50-92	17 (100.0)			
Unemployed	37 (19.0)	16-87	37 (100.0)			
Not Informed	6 (3.1)	20-28	6 (100.0)			
Condom usage						
Always	61 (30.8)	16-60	58 (95.1)	3 (4.9)	1.00	
Intermittent	15 (7.6)	17-64	15 (100.0)			
Never	111 (56.1)	16-90	105 (94.6)	6 (5.4)	0.72 (0.17-2.97)	0.913
Not Informed	11 (5.6)	16-90	11 (100.0)			
Awareness of CMV infection						
None	304 (94.1)	1-92	276 (90.8)	28 (9.2)		
Little	17 (5.3)	5-56	17 (100.0)			
Not Informed	2 (0.6)	17-39	2 (100.0)			

OR = Odds Ratio; CI = Confidence Interval.* people able to writing and reading. ** people unable to read and write. All individuals in both groups literate and illiterate were not attending school.

Table 4. Characteristics of patients positive for CMV IgM Abs.

Hematological Diseases	N	Sex (n)	Age (media)	Occupation (n)	Transfusion * (n)	OR (95% IC)	*p*-value
Anemia of different etiologies	7	F (6) M (1)	46	Retired (1) Autonomous (1) Housewife (3) Student (2)	Yes (3) No (4)	(0.69–5.10)	0.327
ALL	7	F (2) M (5)	29	Housewife (2) Unemployed (5)	Yes (5) No (2)	(0.32–2.32)	0.968
Burkitt's lymphoma	1	M	5	Unemployed	Yes		
Non-Hodgkin's lymphoma	1	M	45	Hemotherapy technician	No		
Thrombocytopenia	1	F	52	House wife	No		

OR = Odds Ratio; CI = Confidence Interval. F = Female; M =Male.

Figures

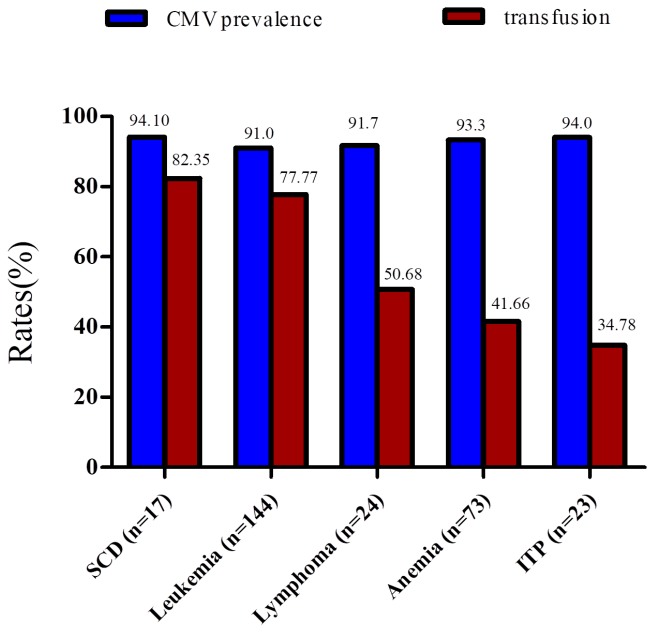

Figure 1

Rates of CMV prevalence and blood transfusions among patients with hematological diseases. All patients subject of this analysis were submitted to more than one blood transfusion during a one-year period. ITP: Immune thrombocytopenic purpura

Figure 2

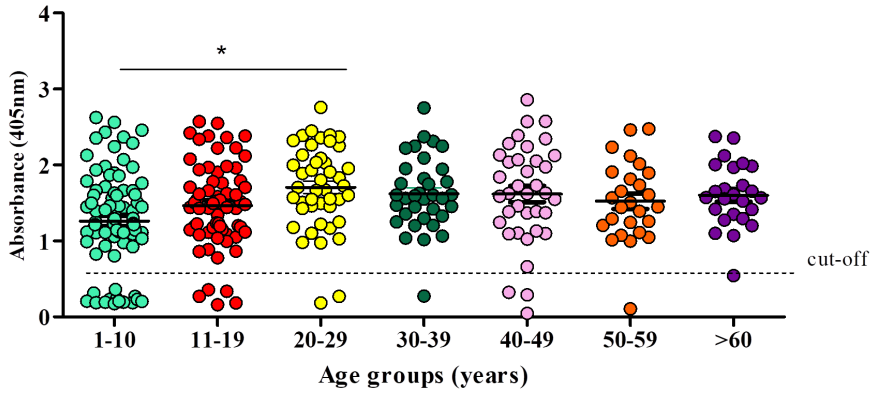

Figure 2

Serum levels of CMV IgG Abs according to the age. (* p = 0.02, One-way ANOVA and Student's t-test).

Figure 3

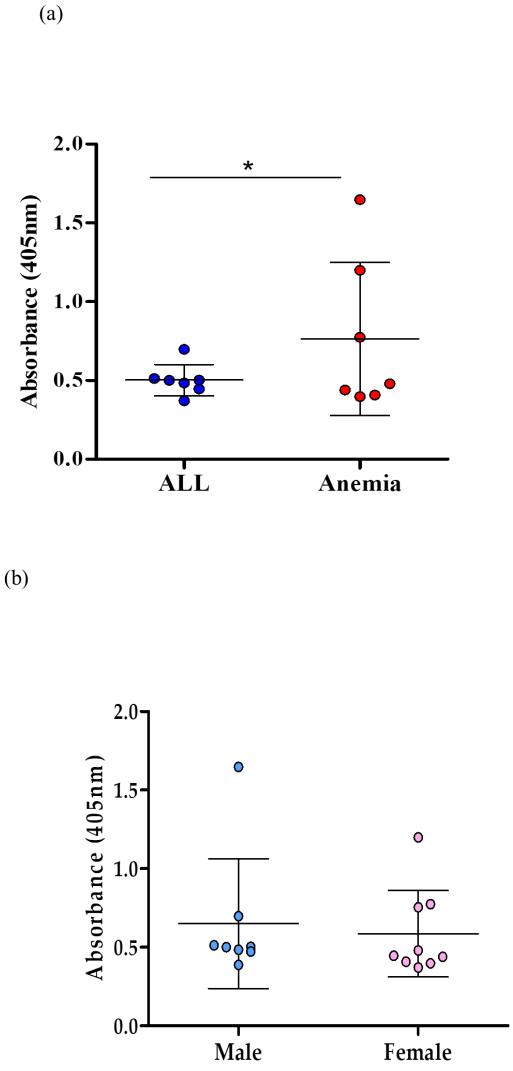

Figure 3

Serum levels of CMV IgM Abs. (a) difference of CMV IgM abs levels between patients with ALL and anemia; (b) Serum CMV IgM abs levels according to sex; * p = 0.001 (F-test).

Figure 4

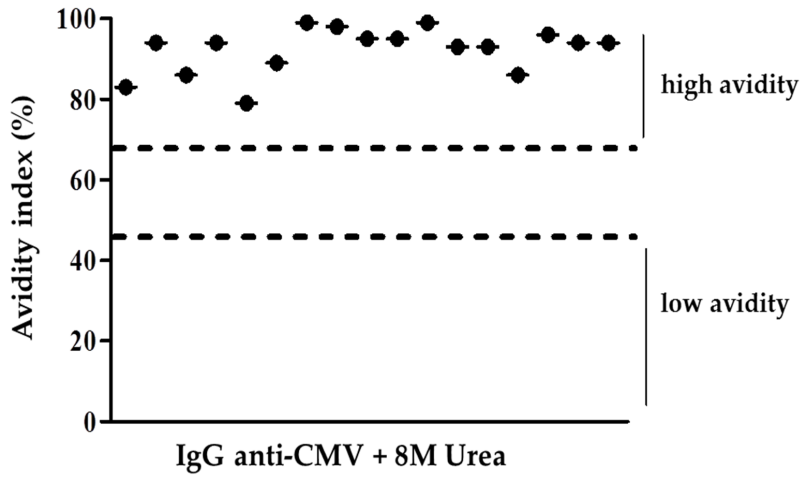

Figure 4

Avidity index values of IgG CMV levels of positive patients to IgM CMV. Low avidity represented by values <45% and high avidity represented by values >65%.

Supplementary Files

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