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RESEARCH ARTICLE

CYTOMEGALOVIRUS INFECTION AMONG LEUKEMIC CHILDREN IN SANA'A CITY, YEMEN

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Abstract

Background and Aims: An investigation into the prevalence of cytomegalovirus (CMV) in children with leukemia at an oncology center in Sana'a city, Yemen, was carried out. CMV is a member of the herpesvirus family and is highly prevalent in the general population. It can cause a potentially fatal latent infection and can reactivate in terms of immune suppression as leukemia.
Materials & Methods: To determine the prevalence of CMV, serum samples were collected from pediatric leukemia patients after diagnosis was confirmed by an oncologist at the Leukemia Center of Kuwait University Hospital, Sana'a, Yemen. A total of 253 pediatric leukemia patients were included in the study, 52.2% were males and 47.8% were females, the mean age of the group was 7.8 ± 3.9 years and the age of the patients ranged from 1 to 16 years. All serum samples were tested for CMV-specific IgG and IgM antibodies using enzyme-linked immunosorbent assay (ELISA) method. Data were analyzed by Epi-Info version 6. Odds ratio and chi-square test were used to compare between categorical variables. Statistical significance was considered as $p < 0.05$.
Results: The prevalence of CMV infection in all participants was 79.1%, with females having a higher prevalence (81.8%) than males (76.5%). The prevalence of CMV current infection (IgM positive) was 6.3%, with females having a 7.4% higher prevalence than males; and age groups 10-14 years had the highest prevalence (9.4%). The study analyzed factors associated with CMV transmission and risk factors for leukemia in pediatric leukemia patients, revealing that 2.8% had other leukemia family members, 91.7% were undergoing chemotherapy, and 2.8% had other diseases.
Conclusion: According to our findings, children with leukemia had a significantly higher prior exposure to CMV. Effective treatment and care practices can help prevent the reactivation of latent viral infections in children with leukemia. Long-term monitoring and additional research are needed to determine the factors that influence the reactivation of latent CMV infection and other latent viral infections in children with leukemia.
Keywords: Cytomegalovirus, pediatric leukemia, seroprevalence, Yemen.

INTRODUCTION

The herpesvirus family includes the cytomegalovirus (CMV). Double-stranded DNA, an icosahedral symmetrical capsid, and a viral envelope make up the virus's genome[1]. By coming into contact with bodily fluids that carry the virus, such as urine, cervical discharge tears, breast milk, seminal fluid, and blood components such leucocyte or saliva, this virus can spread either vertically or horizontally. At the point of entry, the virus causes a primary infection in the mucosal epithelium. As the virus infects and multiplies inside monocytes and CD34+ immature leukocytes of the monocyte lineage, viremia develops[2]. Following an initial infection, CMV, like all herpesviruses, creates a latent infection that lasts a lifetime. Primary infections in immunocompetent individuals either cause no symptoms or a condition resembling mononucleosis. On the other hand, CMV infection frequently results in life-threatening illnesses like pneumonia, gastrointestinal disorders, hepatitis, retinitis, and encephalitis in immunocompromised people, such as

newborns, AIDS patients, and transplant recipients, leading to substantial morbidity and elevated mortality[3]. Furthermore, CMV typically infects people with thalassemia, cancer, dialysis, thyroid disorders, and other chronic illnesses that weaken the immune system[4].

The development of several chronic hematological disorders, including hemoglobinopathies, lymphomas, myelomas, hemophilia, and sickle cell and aplastic anemia, may be significantly influenced by CMV infection[5]. Additionally, because CMV may directly infect megakaryocytes, it can reduce platelet formation. Furthermore, CMV generates a homologue of interleukin (IL)-10 that inhibits ThI immune responses by binding to the IL-10 receptor. Additionally, CMV generates chemokine receptors, which attach to chemokines and suppress cell activity and the immune system[6,7]. Research suggests that CMV may potentially shield tumor cells from the apoptotic process, increasing their resistance to chemotherapy. Additionally, as is typical of herpesviruses, CMV can reactivate after entering a lifelong latent state in specific cell types, such as leucocytes and hematopoietic stem cells[7].

Leukemia is a broad set of hematological illnesses with several subgroups that are physiologically distinct from one another. Leukemia ranks 11th globally in terms of cancer-related morbidity and 10th globally in terms of cancer-related death. Leukemia's precise etiology is yet unknown. Leukemia has been linked to a number of causes, including smoking, genetic mutations, epigenetic lesions, ionic radiation, chemical and other occupational exposures, genetic inheritance, therapeutic medicines, and some viral agents[8,9]. To initiate the leukemogenesis process, more genetic abnormalities are needed[10].

Malignant tumors are a major problem in Yemen, and several studies have been conducted recently on bladder cancer[11], kidney lesions: differentiation between malignant and benign tumors, sex and age distribution and variables associated with renal cell carcinoma[12], clinical and histological analysis of oral and maxillary lesions taken from biopsy[13], prevalence of parotid gland tumors[14], prevalence of central nervous system tumors and histological identification in surgical patients[15], ameloblastoma in the Yemeni population[16], and renal cell tumor (Wilms tumor)[17]. Over the past five years, numerous studies have been conducted on leukemia, including the course of peripheral blood count recovery during induction therapy for childhood acute lymphoblastic leukemia (ALL)[18], hepatitis C virus (HCV) and leukemia: prevalence and risk factors associated with HCV infection among leukemia patients who achieve long-term remission after chemotherapy[19], the main types of childhood leukemia, their clinical signs and outcomes[20], and the clinical presentation of acute leukemia in childhood cancer[21-23]. Several studies have also been conducted to investigate the relationship between viral infections and the development of cancers[19,24,25]. For this reason, this study was conducted to determine the prevalence of CMV infection among children with leukemia, by detecting IgM and IgG antibodies, and to identify potential risk factors for infection with the virus and the possibility of developing an active case in leukemia patients.

MATERIALS AND METHODS

Study design: A cross-sectional study, was carried out in Sana'a City among children with leukemia Cancer in National Oncology Center in Al-Kuwait Hospital, Sana'a City during 2024. The laboratory tests were performed in The National Center of Public Health Laboratory.

Inclusion criteria: All leukemic patients' children of both genders males and females up to 16 years old.

Sample size: The sample size was 253 samples, including all patients visiting the center during the study period.

Sample collection: Two ml of whole blood was collected aseptically from each children's then serum was separated by centrifugation after clotting. The specimens were separate from each sample to Eppendorf tube, then stored at -20°C until tested, then, serum was used in the determination of Cytomegalovirus IgG, and IgM.

Data collection: Data was collected by designing a standard adopted questionnaire for this study that includes details of demographic data, clinical symptoms and lab investigations.

Laboratory tests: Sample was measured by an open system Indirect Enzyme Linked Immune Sorbent Assay (ELISA), for detection Human cytomegalovirus IgM and IgG by a commercially available ELISA (Monobind Inc lake forest, CA 92630, USA)**.**

Statistical analysis: Data were coded and entered into the software to the statistical program and was presented as mean, standard deviation, percentages, tabulation or graphical representation required. The chi-square test was used to find the association between variables. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) version 21.

Ethical consideration: Approval letter was obtained from the Faculty of Medicine and health science-Sana'a University. Consents were taken from all participants and they were informed that participation is voluntary and that they can refuse this without stating any reason. Feedback about the results of the study was given to the participants at the end of the study.

RESULTS

The study included 52.2% males and 47.8% females, the mean age of the group was 7.8±3.9 years and the ages of patients ranged from 1 to 16 years (Table 1). Considering prevalence of CMV-IgG antibodies among different Sex and age groups of 253 leukemia children patients in oncology center, Sana'a city. The crude prevalence of CMV-IgG antibodies was 79.1%, with a 81.8% greater prevalence in females than in males (76.5%). When it came to age groups, the group 5-9 years had the highest prevalence (82.9%) (Table 2).

Table 1: Sex and age distribution of 253 leukemia children patients tested for CMV.

Characters	N (%)
Sex	
Male	132 (52.2)
Female	121 (47.8)
Age in Years	
Less than 5 years	58 (22.9)
5 - 9 years	117 (46.2)
10 – 14 years	64 (25.3)
≥15 years	14 (5.5)
Mean	7.8 years
SD	3.9 years
Median	7 years
Mode	5 years
Min to Max	1-16 years

Table 2: prevalence of CMV-IgG antibodies among different sex and age groups of 253 leukemia children patients.

Characters	N (%)
Sex	
Male n=132	101(76.5)
Female n=121	99 (81.8)
Total positive	200 (79.1)
Age in Years	
Less than 5 years, n=58	40 (70)
5 - 9 years n=117	97 (82.9)
10 – 14 years n=64	50 (78.1)
≥15 years n= 14	13 (92.9)
Mean	8 years
SD	3.9 years
Median	7 years
Mode	5 years
Min to Max	2-16 years

Table 3: Prevalence of CMV-IgM antibodies among different sex and age groups of 253 leukemia children patients.

Characters	N (%)
Sex	
Male n=132	7 (5.3)
Female n=121	9 (7.4)
Total positive	16 (6.3)
Age in Years	
Less than 5 years, n=58	1 (1.7)
5 - 9 years n=117	8(6.8)
10 – 14 years n=64	7 (10.9)
≥15 years n= 14	0 (0.0)
Mean	8.4 years
SD	3.2 years
Median	8 years
Mode	5 years
Min to Max	4-14 years

Reflect on prevalence of CMV-IgM antibodies among different Sex and age groups of 253 leukemia children patients. The crude prevalence of CMV-IgM antibodies was 6.3%, with a 7.4% greater prevalence in females than in males (5.3%). When it came to age groups, the group 10-14 years had the highest prevalence (9.4%) followed by 5-9 years group (6.8%), while for age group ≥15 years it was 0% (Table 3). Respect the concentration of CMV-IgG antibodies among positive leukemia patients, 15.1% of patients had 10.1-20.0 IU/ml, 28.5% had 20.1-40.0 IU/ml, 28% had 40.1-60.0 IU/ml, 26.5% had 60.1-80.0 IU/ml and only 1.5% had ≥ 80.1/ml. The mean amount of CMV-IgG antibodies among the total positive patients was 43.4 IU/ml, and the amount of CMV-IgG antibodies among positive patients ranged from 10.07-82.50 IU/ml (Table 4).

Table 4: Titration of CMV-IgG antibodies among 253 leukemia children patients.

Titration	N (%)
10.1-20.0 IU/ml	31 (15.5)
20.1-40.0 IU/ml	57 (28.5)
40.1- 60.0 IU/ml	56 (28)
60.1 - 80.0 IU/ml	53 (26.5)
≥80.1 /ml	3 (1.5)
Total IgG positive	200 (79.1)
Mean	43.4 IU/ml
SD	19.9 IU/ml
Median	41.1 IU/ml
Mode	41.04 IU/ml
Min to Max	10.07-82.50 IU/ml

Respect the concentration of CMV-IgM antibodies among 16 IgM-positive leukemia patients, 68.8% of patients had 10.1-20.0 IU/ml, 6.3% had 20.1-40.0 IU/ml, 12.6% had 40.1-60.0 IU/ml, 6.3% had 60.1-80.0 IU/ml and 6.3% had ≥80.1/ml. The mean amount of CMV-IgM antibodies among the total positive patients was 27.3 IU/ml, and the amount of CMV-IgM antibodies among positive patients ranged from 10.02-82.04 IU/ml (Table 5).

Table 5: Titration of CMV-IgM antibodies among 253 leukemia children patients.

Titration	N (%)
10.1-20.0 IU/ml	11 (68.8)
20.1-40.0 IU/ml	1 (6.3)
40.1- 60.0 IU/ml	2 (12.6)
60.1 - 80.0 IU/ml	1 (6.3)
≥80.1 /ml	1 (6.3)
Total IgM positive	16 (6.3)
Mean	27.3 IU/ml
SD	25.7 IU/ml
Median	12 IU/ml
Mode	10 IU/ml
Min to Max	10.02-82.04

The most common leukemia among children was acute lymphoblastic leukemia (90.1%), followed by acute myeloid leukemia (9.5%) and chronic myeloid leukemia (CML) in only one case (0.4%). Looking at the time of onset of leukemia, 32% of patients had leukemia between 1–6 months or 7–12 months, 15.4% had leukemia for 13–24 months, 17.8% for 25–60 months and only 2.8% for more than 5 years. The mean duration for the total patients was 17.7 months, with a range of 1–96 months (Table 6). Value, the frequency of factors associated with CMV transmission and risk factors for leukemia in pediatric leukemia patients who tested positive for CMV. Seven (2.8%) patients had other family members with leukemia, 232 (91.7%) had received blood transfusions, none (0.0%) had undergone bone marrow transplantation, 237 (93.7%) leukemia patients were undergoing chemotherapy, 57 (22.5%) had a history of viral infection, 7 (2.8%) had

other diseases, and 5 (2%) leukemia patients had been exposed to radiation (Table 7).

Table 6: Type of leukemia and onset duration for leukemia children patients tested for CMV infections.

Characters	N (%)
Type of leukemia	
ALL	228 (90.1)
AML	24 (9.5)
CML	1 (0.4)
Onset of Leukemia	
1- 6 months	81 (32)
7-12 months	81 (32)
13-24 months	39 (15.4)
25- 60 months (5 years)	45 (17.8)
>5 years	7 (2.8)
Mean	17.7 months
Median	12 months
Mode	12 months
Min - Max	1 -96 months

Considering the clinical signs and symptoms associated with leukemia among pediatric leukemia patients screened for cytomegalovirus. Fever occurred in 95.7%, fatigue and weakness occurred in 96.8%, recurrent infections occurred in 86.2%, weight loss occurred in 63.2%, easy bleeding occurred in 29.2%, recurrent nosebleeds occurred in 34%, red spots on the skin occurred in 62.1%, excessive sweating occurred in 73.1%, bone pain or tenderness occurred in 87.4%, retinitis occurred in 24.1%, and sinusitis, pneumonia, and hepatitis occurred in 15.4%, 33.2%, 2%, 11.5%, and 18.6%, respectively (Table 8). Respect the relationship between gender, age and CMV-IgG antibodies for 253 pediatric leukemia patients in Sana'a City Oncology Center. Female gender was associated with CMV IgG positivity in leukemia patients with an odds ratio of 1.6 with a confidence interval of 0.83–3.2 but no significant *p* value was found as 0.0.12. Considering age groups, age group ≥15 years was associated with CMV IgG positivity in leukemia patients with an odds ratio of 3.6 with a confidence interval of 0.5–75 but no significant *p* value was found as 0.0.19. Also, an odds ratio of 1.5 was found for age group 5–9 years but no significant *p* value was found (0.16).

Table 7: The frequency of associated factors of transmission and infection of CMV and risk factors of leukemia for leukemia children patients tested for CMV infections.

Characters	N (%)
Family leukemia	7 (2.8)
Blood transfusion	232 (91.7)
Bone marrow transplantation	0 (0.0)
Under Chemotherapy	237 (93.7)
History of viral infections	57 (22.5)
Suffering other-disease	7 (2.8)

Table 8: Clinical signs and symptoms associated with leukemia among leukemia children patients tested for CMV.

Signs and symptoms	N (%)
Fever	242 (95.7)
Fatigue and weakness	245 (96.8)
Frequent infections	218 (86.2)
Losing weight	160 (63.2)
Easy bleeding	74 (29.2)
Recurrent nose bleeding	86 (34)
Red spots in skin	157 (62.1)
Excessive sweating	185 (73.1)
Bone pain or tenderness	221 (87.4)
Retinitis	61 (24.1)
Sinusitis	39 (15.4)
Pneumonia	84 (33.2)
Encephalitis	5 (2)
Hepatitis	29 (11.5)
Enteritis	47 (18.6)

Table 9: Associated of sex and age with CMV-IgG antibodies for 253 leukemia children patients.

Characters	IgG + n=200 N (%)	OR	95% CI	X^2	*p*
Sex					
Male, n=132	101(76.5)	0.73	0.37-1.36	1.07	0.3
Female, n=121	99 (81.8)	1.6	0.83-3.2	2.3	0.12
Total positive, n=253	200 (79.1)				
Age in Years					
Less than 5 years, n=58	40 (69)	0.49	0.2-0.99	4.6	0.03
5 - 9 years, n=117	97 (82.9)	1.5	0.8-3.03	1.95	0.16
10 – 14 years, n=64	50 (78.1)	0.93	0.44-1.9	0.04	0.83
≥15 years, n=14	13 (92.9)	3.6	0.5-75	1.7	0.19
Mean	8 years				
SD	3.9 years				
Median	7 years				
Mode	5 years				
Min to Max	2-16 years				

On the other hand, there was no association between CMV IgG positivity and other age groups and male gender. The median age for CMV IgG positivity was 8 years and ranged from 2 to 16 years (Table 9). Considering the association of CMV-IgM antibodies with different Sex and age groups of 253 leukemia children patients. Female gender was associated with CMV IgM positivity in leukemia patients with an odds ratio of 1.4 with a confidence interval of 0.47–4.4 but no significant *p* value was found as 0.48. Considering age groups, age group 10-14 years was associated with CMV IgM positivity in leukemia patients with an odds

ratio of 1.8 with a confidence interval of 0.6–3.1 but no significant *p* value was found as 0.24. Also, an odds ratio of 1.2 was found for age group 5–9 years but no significant *p* value was found (0.75). On the other hand, there was no association between CMV IgM positivity and other age groups and male gender. The median age for CMV IgM positivity was 8.4 years and ranged from 4 to 14 years (Table 10).

Table 10: Association of CMV-IgM antibodies with different sex and age groups of 253 leukemia children patients.

Characters	IgM + n=16 N (%)	*OR*	*95% CI*	X^2	*p*
Sex					
Male, n=132	7 (5.3)	0.7	0.23-2.13	0.49	0.48
Female, n=121	9 (7.4)	1.4	0.47-4.4	0.49	0.48
Total positive, n=253	16 (6.3)				
Age in Years					
Less than 5 years, n=58	1 (1.7)	0.21	0.01-1.6	2.7	0.1
5 - 9 years, n=117	8 (6.8)	1.2	0.39-3.6	0.1	0.75
10 – 14 years, n=64	6 (9.4)	1.8	0.6-3.1	1.3	0.24
≥15 years, n= 14	0 (0.0)	0	0.0-5.6	1.0	0.3
Mean	8.4 years				
SD	3.2 years				
Median	8 years				
Mode	5 years				
Min to Max	4-14 years				

Table 11: Associated confessional risk factors of CMV infection (IgG positive) with type of leukemia and onset duration in leukemia children patients.

Characters	Positive IgG-CMV, n= 200 No (%)	*OR*	*95% CI*	X^2	*p*
Type of leukemia					
ALL, n=228	175 (76.8)	0.0	0.0-0.62	7.4	0.006
AML, n=24	24 (100)	undefined		7.03	0.008
CML, n=1	1 (100)	undefined		0.27	0.6
Onset of Leukemia					
1- 6 months, n=81	65 (80.2)	1.1	0.5-2.3	0.1	0.74
7-12 months, n=81	66 (81.5)	1.25	0.61-2.6	0.42	0.51
13-24 months, n=39	25 (64.1)	0.4	0.18-0.89	6.2	0.01
25- 60 months (5 yrs), n=45	37 (82.2)	1.28	0.52-3.2	0.33	0.56
>5 years, n=7	7 (100)	undefined		1.9	0.16

Table 12: Associated confessional risk factors of CMV infection (IgM positive) with type of leukemia and onset duration in leukemia children patients.

Characters	Positive IgM-CMV, n= 16 No (%)	*OR*	*95% CI*	X^2	*p*
Type of leukemia					
ALL, n=228	12 (5.3)	0.29	0.08-1.1	4.4	0.03
AML, n=24	2 (8.3)	1.4	0.0-7.1	0.18	0.67
CML, n=1	0 (0)	0	0.0-271	0.07	0.93
On set of Leukemia					
1- 6 months, n=81	5 (6.2)	0.96	0.2-3.1	0.0	0.94
7-12 months, n=81	3 (3.7)	0.47	0.1-1.84	1.38	0.23
13-24 months, n=81	3 (3.7)	1.29	0.28-5.2	0.15	0.7
25- 60 months (5 yrs), n=45	3 (6.7)	1.1	0.23-4.2	0.01	0.91
>5 years n=7	1 (14.3)	2.6	0.3-15	0.77	0.38

Worship the risk factors associated with CMV infection (IgG positive) by leukemia type and duration of disease in pediatric leukemia patients. 76.8% of acute lymphoblastic leukemia patients had IgG CMV positive while all (100%) of acute lymphoblastic leukemia patients and chronic lymphocytic leukemia patients had IgG CMV positive. The association of IgG CMV positive with acute lymphoblastic leukemia was 0.0, while for acute lymphoblastic leukemia and chronic lymphocytic leukemia the odds ratio was undetermined. Also for duration of disease, no significant results were found for all periods (Table 11). Table 12 presents risk factors associated with recognition of CMV infection (IgM positivity) by leukemia type and duration of disease in leukemia patients. 5.3% of AML patients had IgM CMV positivity while 8.3% of AML patients had IgM CMV positivity. Taking into account duration of infection, duration of infection greater than 5 years was associated with IgM CMV positivity in leukemia

patients with an odds ratio of 2.6 with a confidence interval of 0.3–15 but no significant p-value was found at 0.38 (Table 12). Considering risk factors associated with cytomegalovirus (IgG positive) infection in pediatric leukemia patients. There was no significant association between cytomegalovirus IgG positivity and the risk factors tested, which included blood transfusion, bone marrow transplantation, chemotherapy, viral infection, other illnesses, and radiation exposure (Table 13).

Table 13: Associated confessional risk factors of CMV infection (IgG positive) with leukemia children patients.

Characters	Positive IgG-CMV, n= 200 No (%)	*OR*	*95% CI*	X^2	*p*
Family leukemia, n=7	7 (100)	undefined		1.9	0.16
Blood transfusion, n=232	180 (77.6)	0.17	0.01-1.3	3.9	0.05
Bone marrow transplantation, n=0	0 (0)	-	-	-	-
Under Chemotherapy, n=237	185 (78.1)	0.24	0.01-1.8	2.2	0.13
History of viral infections, n=57	47 (82.5)	1.3	0.6-3.1	0.52	0.47
Suffering other-disease, n=7	3 (42.9)	0.19	0.03-1.03	5.7	0.01
Radiation exposure, n=5	5 (100)	undefined		1.35	0.24

Respect risk factors associated with cytomegalovirus (IgM positive) infection in pediatric leukemia patients. There was no significant association between cytomegalovirus IgM positivity and the risk factors tested, which included blood transfusion, bone marrow transplantation, chemotherapy, viral infection, other illnesses, and radiation exposure (Table 14).

DISCUSSION

One kind of juvenile cancer that affects youngsters is childhood leukemia, a blood disease. In 2018, 29% of cancer cases in children aged 0-14 years were pediatric leukemia, making it the most prevalent kind of childhood cancer[1]. Acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)[26] are the two most prevalent types of leukemia that affect children. In the current study, the prevalence rate was 52.2% in males and 47.8% in females, the mean age of affected children was 7.8±3.9 years and the patient's ages varied from 1 to 16 years. The results of the current study are comparable to those earlier reported in that leukemia is most commonly diagnosed in children aged 1–14 years, with a mean age of 6 years. There is also an increased prevalence of leukemia in boys compared to girls as shown in our results (52.2% males vs. 47.8% females). Over time, the incidence of children leukemia has been rising, and this year's rate is greater than previous year's. However, this may be due to increased capacity to detect, diagnose, and report the disease, rather than an actual increase in the number of children affected[27,28].

Table 14: Associated confessional risk factors of CMV infection (IgM positive) with leukemia children patients.

Characters	Positive IgM-CMV, n= 16 No (%)	*OR*	*95% CI*	X^2	*p*
Family leukemia, n=7	0 (0)	0	0.0-12.5	0.49	0.48
Blood transfusion, n=232	13 (5.6)	0.36	0.08-0.17	2.5	0.11
Bone marrow transplantation, n=0	0 (0)	-			
Under Chemotherapy, n=237	14 (5.9)	0.44	0.8-3.1	1.1	0.29
History of viral infections, n=57	1 (1.8)	0.22	0.01-1.6	2.6	0.1
Suffering other-disease, n=7	1 (14.3)	2.6	0.36-15.3	0.77	0.38
Radiation exposure, n=5	0 (0)	0.0	0.0-18.8	0.34	0.55

The clinical presentation of acute leukemia is vague and variable which makes it difficult to diagnose[29]. In the current study, considering clinical symptoms in the leukemia patients, fever occurred in 95.7%, fatigue and weakness occurred in 96.8%, recurrent infections occurred in 86.2%, weight loss occurred in 63.2%, easy bleeding occurred in 29.2%, recurrent nosebleeds occurred in 34%, red spots on the skin occurred in 62.1%, excessive sweating occurred in 73.1%, bone pain or tenderness occurred in 87.4%, retinitis occurred in 24.1%, and sinusitis, pneumonia, and hepatitis occurred in 15.4%, 33.2%, 2%, 11.5%, and 18.6%,.

These findings are consistent with the studies of Perveen *et al.* and Kakibuto *et al.*[30,31]. Zaki *et al.*[32], and Shahab and Raziq[33] reported that fever, bleeding and pallor were the main presenting symptoms. These findings could be explained by the mechanism of leukemia as a block of maturation and/or suppression of erythrocytes and polymorphonuclear cells by increased production of blast cells leading to decreased/disturbed production of normal leukocytes/ neutrophils (leading to fever), erythrocytes (leading to anemia/pallor) and platelets (leading to bleeding)[33]. Even though CMV infections are common worldwide, epidemiological surveillance of this virus is still disregarded[34]. It is crucial to increase knowledge about the spread of CMV in Yemen in order to fight the infection and provide clinical care for patients who are immunocompromised, particularly those with hematological disorders like childhood leukemia. Our

results showed that cytomegalovirus (IgG-CMV) infection was highly prevalent among children with leukemia in Sana'a city. The study population showed a higher prevalence (79.1%) than the observed rate (67.6%) in Manaus city, Brazil[35]. Similarly, a study conducted at the Hematology and Hematology Institute of Bahia (HEMOBA), Brazil, observed a higher prevalence of CMV infection (89.4%) in patients with various hematological diseases[36]. Significant seropositivity for CMV infection was also observed in patients from Iran with thalassemia (95.9%) and patients from China with idiopathic lamellar purple (86.4%)[37,38]. Obtained results reveal a widespread prevalence of CMV in the study population and the present study is a pioneer in describing the epidemiology of CMV infection in children with leukemia in Sana'a city, Yemen. In the current study the crude prevalence of CMV-IgG antibodies was 79.1%, with a 81.8% greater prevalence in females than in males (76.5%). When it came to age groups, the group 5-9 years had the highest prevalence (82.9%). The crude prevalence of CMV-IgM antibodies was 6.3%, with a 7.4% greater prevalence in females than in males (5.3%). When it came to age groups, the group 10-14 years had the highest prevalence (9.4%) followed by 5 - 9 years group (6.8%), while for age group ≥15 years it was 0%. We had lower CMV IgG rates than Souza *et al.*[39], and Khameneh *et al.*[40], where the seroprevalence of anti-CMV IgG was 96.4% (95% CI: 95.23 -97.50). However, we had higher IgM rates than Souza *et al.*[39], in donor blood samples, chronic lymphocytic leukemia, and blood donors. Another study by de Melo Silva *et al.*[42], revealed that over 90% of individuals with hematological disorders from the Brazilian western Amazon had CMV infection (IgG positive). In a research by Al-kaabi *et al.*[41], hematological malignancies (93.8%) and 84 control individuals (87.5%) tested positive for CMV IgG, with no statistically significant correlation to blood transfusion history (p value > 0.05). On the other hand, there was a statistically significant association between the CMV IgM positive results in 10 patients (20.8%) and 2 controls (2.1%). The need for leucodepleting filters or CMV-negative blood products is further demonstrated by the increased incidence of CMV infection in individuals with a history of blood transfusions or blood products[42-45]. Also, in the current study, the crude prevalence of CMV-IgG antibodies was 79.1%, with a higher prevalence of 81.8% in females than in males (76.5%). CMV infection tends to be more common in females than in males in many parts of the world. This situation may be due to females being more exposed to CMV because females generally spend more time caring for children at home, as some studies have suggested[34,42]. Obtained results showed that the prevalence of CMV infection was higher in patients with acute myeloid leukemia (100%), which is higher than the reported prevalence for anemia of all causes (93.3%), platelet diseases (94.9%), lymphoma (91.7%), and acute lymphoblastic leukemia (91%) worldwide[43-45].

A recent infection or a recurrent infection (reactivation/ reinfection) may be indicated by the presence of anti-CMV IgM antibodies in serum[46,47]. Rather than reactivation or reinfection, a primary infection is indicated by high IgM and low IgG levels[48]. Since the juvenile leukemia patients in our research had elevated anti-CMV serum IgG levels, all 16 active infections were caused by recurrent infection. Anti-CMV IgM antibody positive rates differ by geography, culture, and demographic. A 3.0% positive percentage for anti-CMV IgM antibodies[49] was found in a sample of American women of reproductive age. Irish pregnant women had a seropositivity rate of 5.9% for CMV IgM antibodies, whereas Croatian hemodialysis patients had a prevalence of 2.3%[50,51]. In Brazil, 1.9% of blood donors from the southern region tested positive for CMV IgM antibodies[52]. The present study found 6.3% seropositivity for CMV IgM antibodies in the study sample, which is higher than most rates described elsewhere[35]. These findings suggest that leukemias may lead to CMV recurrence.

In the context of childhood leukemia, recurrent CMV infection has been associated with immunosuppression induced by treatment regimens. This is similar to the finding of Elgarten *et al.*[53], who observed a high rate of CMV reactivation (84.6%) in children with hemoglobinopathies who underwent hematopoietic stem cell transplantation and immunosuppressive therapy with alemtuzumab[53]. Similar to earlier reports elsewhere, the rate of anti-CMV IgM antibodies was 5.3% in ALL and 8.5% in AML, indicating CMV reactivation[54-58]. CMV reactivation is considered high in individuals with leukemia. Equally high rates of CMV reactivation were observed in patients from India (11.3%) and Iraq (12%) with leukemia[54,55]. Another study observed CMV reactivation in 66% of CLL patients, after treatment with alemtuzumab[53,56]. These studies suggest that leukemia increases the risk of recurrent CMV infection through unknown mechanisms. However, natural killer cells have been recognized as a key factor in combating CMV infection[57]. One risk factor for CMV reactivation is NK cell abnormalities or deficiencies[58]. Given that NK cell abnormalities have previously been documented in leukemia patients[59], this may help to explain the increased rate of CMV reactivation among patients with acute lymphoblastic leukemia and AML that has been observed in our study and elsewhere. To examine this connection, we did not assess the NK cell phenotype in individuals who tested positive for anti-CMV IgM in this research. However, our results raise the following questions: Are patients with ALL and AML at higher risk for CMV recurrence? Are recurrence rates associated with immunosuppression states induced by ALL and AML leukemia? A longitudinal study with a larger sample size is needed to answer these questions. Taken all together, our findings bring a new understanding of the epidemiological profile of CMV infection in leukemia children patients from Sana'a city. The data presented here may serve as a starting point for future studies, particularly those seeking to clarify the negative impact of predicting CMV infection in leukemia patients. In the current study, female sex was associated with CMV IgG positivity in leukemia patients, with an odds ratio

of 1.6. The odds ratio for age groups ≥ 15 years was 1.5, but no significant *p* value was found. Our study suggests that seroprevalence increases with age and female sex. This study was CMV positive, which is comparable to previous studies in t United States[52,60-64]. It is also important to understand the personal factors, exposures, and behaviors that may be associated with increased CMV infection.

In the current study, there was no significant association between CMV IgG positivity and the risk factors tested, which included blood transfusion, bone marrow transplantation, chemotherapy, viral infection, other diseases, and radiation exposure. This finding differs from those reported elsewhere among different patient groups or the general population[52]. Although risk factors for CMV infection have been evaluated previously, among different patient groups with autoimmune diseases or solid cancer patients, and patients with blood disorders, there are no or few data regarding risk factors associated with CMV acquisition among leukemia patients[35,65].

Limitations of the study

The study relied on identifying cytomegalovirus (CMV) presence in leukemia patients using the presence of CMV antibodies, which does not confirm active infection. It would have been preferable and necessary to diagnose the virus using the pp65 antigen blood test or the CMV-DNA viral load test. Therefore, more accurate future studies using the pp65 antigen blood test or the CMV-DNA viral load test are needed to provide more comprehensive results and include a larger sample of patients.

CONCLUSIONS AND RECOMMENDATIONS

Recurrent infection is more common in patients with acute lymphoblastic leukemia (ALL) or acute myelogenous leukemia (AML), and CMV infection was highly prevalent in the study group. Age and female sex were factors that were plausibly associated with CMV infection. In summary, this study provides new findings on the epidemiology of CMV infection by serologically characterizing this infection in children with leukemia in Sana'a city, Yemen. Our findings showed that the risk factors examined blood transfusion, bone marrow transplantation, chemo-therapy, viral infection, other illnesses, and radiation exposure did not significantly correlate with CMV IgG positivity, nor did they correlate with a higher risk of CMV infection in the study group. Since there isn't already a mechanism for CMV monitoring, these findings could help the Ministry of Health monitor CMV infections. They might also serve as a new foundation for more thorough future research that includes individuals with other hematological disorders.

Avoid the emergence of cytomegalovirus in leukemia patients or in case of emergence of cytomegalovirus in this group of patients, the correct diagnosis and treatment is necessary as soon as possible to avoid the consequences of infection with cytomegalovirus in these immunocompromised patients. Cytomegalovirus infection can be prevented by preventive treatment and early diagnosis can be made by blood antigen pp65 or viral load DNA-CMV. Correct treatment with adjusted doses and continuing treatment until the infection is eliminated is very important to avoid cytomegalovirus disease and resistance to antiviral therapy. More comprehensive future studies should be conducted that include patients with other blood diseases.

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AUTHOR'S CONTRIBUTION

Amirh Abdullah Sa'aed Aljabri: writing original draft, methodology, investigation. **Okbah A:** formal analysis, data curation, conceptualization. **Alhadi AM:** writing, review and editing, methodology. **Al-Shamahi E, Al-Hababi N, Al-Haidary N:** formal analysis, data curation, conceptualization. Final manuscript was checked and approved by all authors.

DATA AVAILABILITY

The accompanying author can provide the empirical data that were utilized to support the study's conclusions upon request.

CONFLICT OF INTEREST

There is no conflict of interest associated with this study.

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