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Seroprevalence of Human cytomegalovirus (HCMV) in Cancer Patients Undergo Chemotherapy in Taiz City, Yemen

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مدى إنتشار الفيروس المضخم للخلايا في الأشخاص الذين يعانون من السرطان ويخضعون للعلاج الكيميائي في محافظة تعز - اليمن

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الملخص

الفيروس المضخم للخلايا (CMV)، وهو فيروس بيتا هربس يتواجد في كل مكان، قادر على البقاء في الجسم بصورة كامنة مدى الحياة بعد الإصابة الأولية. يعد الفيروس المضخم للخلايا (CMV) أحد مسببات الأمراض الانتهازية على نطاق واسع، والذي يمكن أن يسبب عدوى بدون أعراض لدى الأشخاص الأصحاء، ولكنه مرض يهدد الحياة في الأفراد الذين يعانون من نقص المناعة. أثناء العدوى الاولية الفيروس المضخم للخلايا أو في حالة إعادة التنشيط للاصابة الكامنة بالفيروس، يكون العديد من الأفراد معرضين لخطر الإصابة بأمراض خطيرة مثل متلقي زرع الخلايا الجذعية المكونة للدم الخيفي، ومتلقي زراعة الأعضاء الصلبة؛ مرضى السرطان الذين يخضعوا مرضى للعلاج الكيميائي، والمرضى الذين يتلقون العلاج بالستيرويد، ومرضى فيروس نقص المناعة البشرية، والمواليد من امهات مصابة بالفيروس. يصنف السرطان على أنه السبب الثاني للوفاة على مستوى العالم بعد أمراض القلب والأوعية الدموية حيث تم الإبلاغ عن 9.6 مليون حالة وفاة في جميع أنحاء العالم.

هدفت هذه الدراسة إلى تحديد معدل الانتشار المصلي العام للفيروس المضخم للخلايا بين مرضى السرطان الذين يخضعون للعلاج الكيميائي. بالإضافة إلى ذلك، حددت عامل الخطر المرتبط بإعادة تنشيط الفيروس المضخم للخلايا وربط إعادة تنشيط الفيروس المضخم للخلايا بأنواع العلاج الكيميائي.

الكلمات المفتاحية: الفيروس المضخم للخلايا، السرطان، العلاج الكيميائي، تعز، اليمن.

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Abstract

Cytomegalovirus (CMV), a ubiquitous beta-herpesvirus, is able to establish lifelong latency after initial infection. CMV is a widespread opportunistic pathogen, which can cause asymptomatic infection in healthy people but life-threatening disease in immunosuppressed individuals. During CMV primary CMV infection or reactivation, many individuals are at a high risk of development severe diseases such as allogeneic hematopoietic stem cell transplant recipients, solid organ transplant recipients; cancer patients undergo chemotherapy, patients receiving steroid therapy, HIV patients and, baby of infected mother. Cancer is classified as a second cause of death globally after cardiovascular diseases with 9.6 million deaths were reported worldwide.

This study aimed at determining the overall seroprevalence of CMV among cancer patients who undergo chemotherapy. In addition, it identified the risk factor associated with CMV reactivation and to link the CMV reactivation with types of chemotherapy.

In this study, 200 randomize blood samples were collected from cancer patients undergoing chemotherapy who attended to Al Amal center for the treatment of cancer patients in Taiz city. Samples were tested for detection of CMV IgG antibodies by electrochemiluminescence (ECLIA) method.

The overall seroprevalence of CMV in cancer patients was 99.5%, CMV prevalence was 100% and 99% in solid cancer and, hematological malignancy respectively. Seroprevalence of HCMV regarding gender in male 100% and in female 99%. The prevalence of HCMV was 100% in all age groups except the age group 16-30 years 96%. Seroprevalence of HCMV regarding history of blood transfusion was 56.5%. Seroprevalence of HCMV regarding radiotherapy was 100%. Seroprevalence of HCMV regarding chemotherapy drugs was 99.2%.

CMV reactivation among cancer patients was approved by this study. Therefore, CMV detection assay must include in the list of screening test that recommended for solid cancer and hematological malignancies patients underwent chemotherapy as well as for blood bag given to cancer patients undergo chemotherapy should be taken from seronegative CMV donors.

Keywords: Human cytomegalovirus, Cancer, Chemotherapy, Taiz, Yemen.

Introduction:

Human Cytomegalovirus (HCMV), officially referred to as human herpesvirus 5 (HHV5), is an omnipresent virus which was discovered in the1950s (Cannon *et al*., 2010). HCMV is species specific, humans beings are believed to be the only reservoir for CMV (Murphy & Shenk, 2008; Mocarski *et al*., 2012). Natural transmission of the virus occurs by direct or indirect person to person in several different ways, all requiring close contact with virus bearing material. including kissing, saliva, and nasal discharge on the hands or urine, (Dupont & Reeves, 2016). Moreover, it has been shown that CMV spreads through sexual contacts, blood transfusions and solid organ transplantation (SOT). Usually, the first exposure to CMV occurs during childhood, which is often asymptomatic. In healthy individuals, primary CMV infection is usually subclinical. But CMV has been implicated in a variety of diseases in healthy persons infectious mononucleosis like (IMN) disease (Klenerman & Oxenius, 2016) include, persistent fever, malaise, muscle pain, leukopenia, neutropenia, lymphopenia, thrombocytopenia and lymphadenopathy or evidence of tissue invasion e.g., pneumonitis, hepatitis, retinitis, gastrointestinal disease (Humar & Snydman, 2009; Nyholm & Schleiss, 2010; Swanson & Schleiss, 2013). Similar to other herpesviruses, CMV establishes a life-long latency and cannot be cleared by the immune system (Griffiths *et al*., 2015; Dupont & Reeves, 2016). Reactivation of latent CMV occurred after many years spontaneously or by any number of stimuli response, or when cell mediated immunity (CMI) defenses are impaired releasing intact virions that can infect new cells and cause CMV disease (Zhang *et al*., 2014; Griffiths *et al*., 2015; Goodrum, 2016).

Potential groups at risk of severe diseases from either primary CMV infection or reactivation of latent CMV infection include allogeneic hematopoietic stem cell transplant (aHSCT) recipients, SOT recipient (SOTR), solid tumors (ST), hematologic malignancies (HM) who are receiving chemotherapy, immunosuppressed patients receiving steroid therapy, baby from infected mothers and those with Acquired Immune Deficiency Syndrome (AIDS) (Atkinson & Emery, 2011; Walton *et al*., 2014; Mestas & Forsythe, 2016).

Cancer is the second leading cause of death worldwide after cardiovascular disease, with 9.6 million deaths reported worldwide in 2018

(Bray *et al*., 2018; Ferlay *et al*., 2019; WHO, 2020). According to the estimate of World Health Organization, (WHO), it has been estimated that there were more than 14 million new cases worldwide *(Stewart & Wild, 2014; Siegel et al*., 2018; Ferlay *et al*., 2019). Various studies have identified high incidence of active CMV infection in tumor tissues including breast cancer (BC), gastric cancer (GC), colorectal cancer (CRC), glioblastoma (GMB), medulloblastoma (MB), prostatic cancer (PCs), ovarian cancer (OV), cervix cancer (CC), and HM, (Cobbs *et al*., 2002; Cox *et al*., 2010; Harkins *et al*., 2010; Baryawno *et al*., 2011; Wolmer-Solberg *et al*., 2013; Taher *et al*., 2014; Luo *et al*., 2018; Meng *et al*., 2018; Paradowska *et al*., 2019). The, growing use of cytoreductive therapy that obviously represses cellular immunity is ratify to be one of the key factors that expose patients to a greater risk of severe CMV disease (Piiparinen *et al*., 2002).

Further, death attributable to CMV was reported in 42% of HM and ST manifestation (Wang *et al*., 2011). In addition, in ST patients, CMV disease, reported a mortality rate of 61% (Wang *et al*., 2011). Moreover, the mortality rate from CMV disease was reported as high as 57% in patients with leukemia and up to 90% in those who had undergone HSCT, (Mattes *et al*., 2005). Risk of CMV disease development in patients with oncological hematological diseases increases when anti-cancer drugs with T-suppressive effect are used, (e.g, high cyclophosphamide doses, methotrexate or corticosteroids) (Nguyen *et al*., 2001) or alemtuzumab, rituximab or fludarabine (Nguyen *et al*., 2002; Gallamini *et al*., 2007). Unfortunately, infectious complications problem associated with CMV reactivation in cancer patient undergo chemotherapy need to be evaluated.

This study aims at determining the CMV seroprevalence among cancer patients undergo chemotherapy in Al- Amal Center for Treatment Of Oncology Patients. Taiz City Yemen and to identify the risk factor associated with CMV reactivation. In addition to link the CMV reactivation with types of chemotherapy.

Material and Methods:

It was a cross sectional; retrospective study of cancer patients undergo chemotherapy treated at the Al- Amal Centre for the treatment of cancer patients in Taiz city Yemen between August 2021 to February 2023. In this

study, 200 cancer patients randomly were selected from a total of 8765 cancer patients attending Al- Amal Center in Taiz city Yemen during the study period. The amount of 5 ml blood samples were collected into a sterile anticoagulated bottle (red cup tube) and allowed to clotted for 30 minutes. After clot formed the samples were centrifuged, at 4300 g for 5 minutes, serum was separated into a sterile Eppendorf on each collection day for storage at -20 °C until the required sample size was obtained, for Cobas testing. Detection of CMV IgG antibodies by electrochemiluminescence (ECLIA) by Cobas e 411. All the relevant collected data were analyzed by using IMB Statistical Package for Social Sciences (SPSS) version 24 bivariant correlation. The subgroup was analyzed for risk factor identification by using student t test, one way ANOVA.

Results:

Seroprevalence of HCMV in Cancer patients undergo chemotherapies

The overall seroprevalence of HCMV in cancer patients was 99.5%. Among 200 patients undergo chemotherapy, 93 samples (46.5%) were males and 107 (53.5%) were females (Table 1) with no significance differences between both genders. They were at the same risk of HCMV reactivation.

According to cancer types, 157 (78.5%) patients were diagnosed with solid cancer and 43 (21.5%) with HC. There were significant differences in HCMV reactivation in different types of cancer (P. value = 0.055) (Table 1).

According to the patients' age, there were six groups. Most of the patients (32%) were at 46-60 years old. In the first period 1-15 years 18 patients (9%), in 16-30 years 25 patients (12.5%), in 31-45 years 46 patients (23%), in 46-60 years there were 64 patients (32%), in 61-75 years 35 patients (17.5%), finally, in group 6 or 75-90 years there were 12 patients (6%). All the age groups were at the risk of HCMV reactivation (Table 1).

Based on the history of blood transfusion 114 (57%) had transfused blood, with 30 patients 15% had transfuse of one blood bag whereas one patient 0.5% had transfuse of 200 blood bags. There were no significant differences in seroprevalence of HCMV reactivation in cancer patients regarding blood transfusion (P. value = 0.384) (Table 1).

Table (1): Seroprevalence of HCMV among chemotherapy patients

Gender	N	%	Seroprevalence of HCMV		P. value
			N	%	
Male	93	46.5	93	100	0.350
Female	107	53.5	106	99	
Type of Cancer					
Solid tumor	157	78.5	157	100	0.055
Hematological malignencies (HM)	43	21.5	42	97.7	
Age group					
1-15	18	9	18	100	0.218
16-30	25	12.5	24	96	
31-45	46	23	46	100	
46-60	64	32	64	100	
61-75	35	17.5	35	100	
76-90	12	6	12	100	
Blood Transfusion					
Yes	114	57	113	56.5	0.384
No	86	43	86	43	

There were significant differences in seroprevalence of HCMV reactivation in cancer patients regarding to number of blood transfusion (P. value 0.000) (Table 2).

Table (2): Seroprevalence of HCMV among chemotherapy patients according blood transfusion

Number of blood transfusion	Seroprevalence of HCMV				P. value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
0.00	85	42.5	0	0	0.000
1	30	15	0	0	
2	23	11.5	0	0	
3	13	6.5	0	0	
4	9	4.5	0	0	
5	9	4.5	0	0	
6	8	4	0	0	
7	1	0.05	0	0	
8	2	1	0	0	
10	2	1	0	0	
11	1	0.05	0	0	
12	2	1	0	0	
14	1	0.05	0	0	
15	4	2	0	0	
20	3	1.5	0	0	
25	2	1	0	0	
30	1	0.05	1	0.05	
40	1	0.05	0	0	
60	1	0.05	0	0	
200	1	0.05	0	0	

Among 200 patients, only one patient (0.5%) had previous organ transplantation (renal transplantation) and no significance differences between seroprevalence of HCMV and organ transplantation (Table 3). Regarding types of treatment, 29 (14.5%) of patients underwent radiotherapy were, and 171 patients (85.5%) not attended to radiotherapy with no significance differences between seroprevalence of HCMV and radiotherapy. While only 2 patients (1%) were taken steroid therapy and the reminder 198 (99%) of patients were without steroid therapy and no significance differences between seroprevalence of HCMV and steroid therapy (Table 3). Supportive treatment with antiviral prophylactic were used in 28 patients (14%) and 172 patients (86%) without supportive treatments. There were no significance differences in seroprevalence of HCMV reactivation in cancer patients regarding to antiviral prophylactics P. value (0.686) (Table 3).

Table (3): Seroprevalence of HCMV among chemotherapy patients according to Organ Transplantation, Radiotherapy, Steroid therapy, Antiviral prophylactics

Organ Transplantation	N	%	Seroprevalence of HCMV		P. value
			N	%	
Yes	1	0.05	1	100	0.943
No	43	199	198	99.5	
Radiotherapy					
Yes	29	14.5	29	100	0.680
No	171	85.5	170	99.4	
Steroid therapy					
Yes	2	1	2	100	0.920
No	198	99	197	99.5	
Antiviral prophylactics					
Yes	28	14	28	100	0.686
No	172	86	171	99.4	

Results of Correlation between CMV reactivation and types of chemotherapy

From 200 cancer patients 131 patients (65.5%) underwent chemotherapy and 69 patients (34.5%) did not take chemotherapy treatment with no significant differences between seroprevalence of HCMV and chemotherapy used (P. value = 0.467).

Table (4). Seroprevalence of HCMV among chemotherapy patients according to number of chemotherapy drugs

Chemotherapy	N	%	Seroprevalence of HCMV		P. value
			N	%	
Yes	131	66.5	130	99.2	0.467
No	69	34.5	69	100	

No significance correlation between HCMV reactivation and type of chemotherapy used except there was significance correlation with Methotrexate 50 mg I.V (P.value = 0.009) and Methotrexate 50 mg intrathecal (P. value = 0.017) (Table 5).

Table (5): Correlation between HCMV seropositivity and type of chemotherapy drugs

No	Type of drug	Take	N	%	Seroprevalence of HCMV among Chemotherapy Patients				P-value
					HCMV Seropositive		HCMV Seronegative		
					N	%	N	%	
1	Bleomycin 15 mg	Yes No	8 192	4 96	8 191	4 95.5	0 1	0 0.05	0.839
2	Cyclophosphamid 200 mg	Yes No	23 177	11.5 88.5	23 176	11.5 88	0 1	0 0.05	0.719
3	Cyclophosphamid 500 mg	Yes No	21 179	10.5 89.5	21 178	10.5 89	0 1	0 0.05	0.733
4	Cyclophosphamid 1000 mg	Yes No	33 167	16.5 83.5	33 166	16.5 83	0 1	0 0.05	0.658
5	Docetaxel 120 mg	Yes No	5 195	2.5 97.5	5 194	2.5 97	0 1	0 0.05	0.873
6	Docetaxel 20 mg	Yes No	4 196	2 98	4 195	2 97.5	0 1	0 0.05	0.887
7	Docetaxel 80 mg	Yes No	17 183	8.5 91.5	17 182	8.5 91	0 1	0 0.05	0.761
8	Doxorubcin 50 mg	Yes No	45 155	22.5 77.5	45 154	22.5 77	0 1	0 0.05	0.591
9	Doxorubcin 10 mg	Yes No	28 172	14 86	28 171	14 85.5	0 1	0 0.05	0.688
10	Epirubicin 50 mg	Yes No	1 199	0.05 99.5	1 198	0.05 99	0 1	0 0.05	0.944
11	Etopside 100 mg	Yes No	13 187	6.5 93.5	13 186	6.5 93	0 1	0 0.05	0.793
12	Fluorouracil 250 mg	Yes No	4 196	2 98	4 195	2 97.5	0 1	0 0.05	0.887
13	Fluorouracil 500 mg	Yes No	31 169	15.5 84.5	31 168	15.5 84	0 1	0 0.05	0.670
14	Methotrexate 50 mg I.V	Yes No	26 174	13 87	25 174	12.5 87	1 0	0.05 0	0.009
15	Methotrexate 50 mg Intrathecia	Yes No	30 170	15 85	29 170	14.5 85	1 0	0.05 0	0.017
16	Paclitaxel 30 mg	Yes No	20 180	10 90	20 179	10 89.5	0 1	0 0.05	0.740
17	Paclitaxel 100 mg	Yes No	46 154	23 77	45 154	22.5 77	1 0	0.05 0	0.591
18	Paclitaxel 150 mg	Yes No	18 182	9 91	17 182	8.5 91	1 0	0.05 0	0.761
19	Paclitaxel 260 mg	Yes No	27 173	13.5 86.5	26 173	13 86.5	1 0	0.05 0	0.699
20	Epirubicin 10 mg	Yes No	0 200	0 100	0 0	0 0	0 0	0 0	0.00

Different chemotherapy drugs were with patients and there was a significant correlation between HCMV reactivation and number of Bleomycin 15 mg doses (P. value = 0.000) (Table 6)., number of Cyclophosphamide 200 mg doses (P. value = 0.000), 500 mg, and 1000 mg doses (P. value = 0.000) (Table 7).

Table (6): Correlation between HCMV seropositivity and number of Bleomycin doses

Number of Bleomycin 15 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	1	0.05	0	0	0.000
2 doses	0	0	0	0	
3 doses	0	0	0	0	
4 doses	1	0.05	0	0	
5 doses	0	0	0	0	
6 doses	1	0.05	0	0	
7 doses	1	0.05	0	0	
8 doses	1	0.05	0	0	
9 doses	1	0.05	0	0	
10 doses	0	0	0	0	
11 doses	1	0.05	0	0	
12 doses	1	0.05	0	0	

Table (7): Correlation between HCMV seropositivity and number of Cyclophosphamide doses

Number of Cyclophosphamide 200 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	10	5	0	0	0.000
2 doses	8	4	0	0	
3 doses	1	0.05	0	0	
4 doses	4	2	0	0	
Number of Cyclophosphamide 500 mg doses					
1 dose	10	5	0	0	0.000
2 doses	6	3	0	0	
3 doses	2	1	0	0	
4 doses	1	0.05	0	0	
5 doses	2	1	0	0	
Number of Cyclophosphamide 1000 mg doses					
1 dose	6	3	0	0	0.00
2 doses	13	6.5	0	0	
3 doses	4	2	0	0	
4 doses	8	4	0	0	
5 doses	0	0	0	0	
6 doses	2	1	0	0	

Using Docetaxel doses in the treatment showed that there was a significant correlation between HCMV reactivation and number of Docetaxel 120 mg, 20 mg, 80 mg, 50 mg doses (P. value = 0.000) (Table 8).

Table (8): Correlation between HCMV seropositivity and number of Docetaxel doses

Number of Docetaxel 120 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	2	1	0	0	
2 doses	3	1.5	0	0	0.000
Number of Docetaxel 20 mg doses					
1 dose	1	0.05	0	0	
2 doses	0	0	0	0	
3 doses	0	0	0	0	
4 doses	1	0.05	0	0	0.000
5 doses	0	0	0	0	
6 doses	0	0	0	0	
7 doses	2	1	0	0	
Number of Docetaxel 80 mg doses					
1 dose	6	3	0	0	
2 doses	4	2	0	0	
3 doses	2	1	0	0	
4 doses	1	0.05	0	0	
5 doses	1	0.05	0	0	0.000
6 doses	2	1	0	0	
7 doses	0	0	0	0	
8 doses	1	0.05	0	0	

Moreover, during treatment with Doxorubicin 50 mg doses, there was a significant correlation between HCMV reactivation and number of Doxorubicin 50 mg, 10 mg doses (P. value = 0.000) (Table 9).

Table (9): Correlation between HCMV seropositivity and number of Doxorubicin doses

Number of Doxorubicin 50 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	13	6.5	0	0	
2 doses	4	2	0	0	
3 doses	7	3.5	0	0	
4 doses	9	4.5	0	0	
5 doses	5	2.5	0	0	
6 doses	2	1	0	0	0.000
7 doses	0	0	0	0	
8 doses	1	0.05	0	0	
9 doses	2	1	0	0	
10 doses	2	1	0	0	

Number of Doxorubicin 50 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
Number of Doxorubicin 10 mg doses					
1 dose	8	4	0	0	0.000
2 doses	11	5.5	0	0	
3 doses	5	2.5	0	0	
4 doses	1	0.05	0	0	
5 doses	2	1	0	0	
6 doses	1	0.05	0	0	

There was only one patient received Epirubicin 50 mg therapy and statistical differences between HCMV reactivation and number of Epirubicin 50 mg doses cannot be calculated, (Table 10), Whereas there was a significance correlation between HCMV reactivation and number of Etoposide 100 mg doses (P. value = 0.000) (Table 10).

Table (10): Correlation between HCMV seropositivity and number of Epirubicin or Etoposide doses

Number of Epirubicin 50 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
Single dose	1	0.05	0	0	
Number of Etopside 100 mg doses					
1 dose	0	0	0	0	0.000
2 doses	1	0.05	0	0	
3 doses	4	2	0	0	
4 doses	6	3	0	0	
5 doses	0	0	0	0	
6 doses	2	1	0	0	

Two doses of Fluorouracil (250 mg and 500 mg) were used with patients with a significant correlation, between HCMV reactivation and number of them (P. value = 0.000) (Table 11).

Table (11): Correlation between HCMV seropositivity and number of Fluorouracil 250 mg doses

Number of Fluorouracil 250 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	2	1	0	0	
2 doses	2	1	0	0	0.000
Number of Fluorouracil 500 mg doses					
1 dose	5	2.5	0	0	
2 doses	8	4	0	0	
3 doses	4	2	0	0	0.000
4 doses	2	1	0	0	

Number of Fluorouracil 250 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
5 doses	2	1	0	0	
6 doses	4	2	0	0	
7 doses	2	1	0	0	
8 doses	1	0.05	0	0	
9 doses	2	1	0	0	
10 doses	1	0.05	0	0	
11 doses	0	0	0	0	
12 doses	2	1	0	0	

Similarly, Methotrexate used with dose 50 mg IV or intrathecal. Only patients treated with Methotrexate IV showed statistically difference result (P. value= 0.013) (Table 12).

Table (12): Correlation between HCMV seropositivity and number of Methotrexate doses

Number of Methotrexate 50 mg IV doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	4	2	0	0	
2 doses	7	3.5	0	0	
3 doses	2	1	0	0	
4 doses	2	1	0	0	
5 doses	5	2.5	0	0	
6 doses	1	0.05	0	0	
7 doses	1	0.05	0	0	0.013
8 doses	0	0	0	0	
9 doses	0	0	0	0	
10 doses	2	1	0	0	
11 doses	1	0.05	0	0	
12 doses	0	0	1	0.05	
Number of Methotrexate 50 mg intrathecal doses					
1 dose	4	2	0	0	0.988
2 doses	2	1	0	0	
3 doses	0	0	0	0	
4 doses	2	1	0	0	
5 doses	1	0.05	0	0	
6 doses	1	0.05	0	0	
7 doses	1	0.05	0	0	
8 doses	4	2	1	0.05	
9 doses	4	2	0	0	
10 doses	2	1	0	0	
11 doses	1	0.05	0	0	
12 doses	3	1.5	0	0	
13 doses	1	0.05	0	0	
14 doses	2	1	0	0	
15 doses	1	0.05	0	0	

On other hand, all patients treated with Paclitaxel 4 doses (30 mg, 100 mg, 150 mg and 260 mg) showed reactivation of HCMV with significant differences (P. value= 0.000) (Table 13).

Table (13): Correlation between HCMV seropositivity and number of Paclitaxel doses

Number of Paclitaxel 30 mg doses	Seroprevalence of HCMV among Chemotherapy Patients				P-value
	HCMV Seropositive		HCMV Seronegative		
	N	%	N	%	
1 dose	7	3.5	0	0	0.000
2 doses	2	1	0	0	
3 doses	5	2.5	0	0	
4 doses	1	0.05	0	0	
5 doses	2	1	0	0	
6 doses	2	1	0	0	
7 doses	0	0	0	0	
8 doses	0	0	0	0	
9 doses	0	0	0	0	
10 doses	1	0.05	0	0	
Number of Paclitaxel 100 mg doses					
1 dose	6	3	0	0	0.000
2 doses	7	3.5	0	0	
3 doses	8	4	0	0	
4 doses	10	5	0	0	
5 doses	3	1.5	0	0	
6 doses	3	1.5	0	0	
7 doses	2	1	0	0	
8 doses	2	1	0	0	
9 doses	0	0	0	0	
10 doses	2	1	0	0	
11 doses	0	0	0	0	
12 doses	1	0.05	0	0	
13 doses	0	0	0	0	
14 doses	1	0.05	0	0	
Number of Paclitaxel 150 mg doses					
1 dose	7	3.5	0	0	0.000
2 doses	6	3	0	0	
3 doses	2	1	0	0	
4 doses	2	1	0	0	
Number of Paclitaxel 260 mg doses					
1 dose	8	4	0	0	0.000
2 doses	2	1	0	0	
3 doses	8	4	0	0	
4 doses	7	3.5	0	0	
5 doses	1	0.05	0	0	

Discussion:

This study shows a high seroprevalence HCMV reactivation among cancer patients undergo chemotherapy in Yemen. The overall seroprevalence of HCMV IgG was 99.5%, this result was confirmed by various studies over the world. Another three studies that revealed that in all explored cancers the prevalence of HCMV was close to 100% are *(Forslund et al., 2014; Huang et al*., 2014; Yamashita *et al*., 2014).

The results of this study showed that both genders are at the same risk of HCMV reactivation. This result was confirmed by various studies such as Al-Toban and his group in 2018, and Loutfy and his colleagues in 2006, and 2017. They demonstrated that there was no significant difference in the sex of ALL patients and HCMV viremia in Iraq and Egypt (Loutfy *et al*., 2006; Loutfy *et al*., 2017; Al-Toban *et al*., 2018). On the contrary of this result, there were several researches that claimed that seroprevalence of HCMV in women is higher than that reported in men. For instance, Han in 2007 reported that HCMV antigenemia in cancer patients was higher in women (Han, 2007; Hyde *et al*., 2010; Jones, 2013).

The association of HCMV and cancer was investigated in several studies all over the world. Carlos Cobbs (2002) carried the earlier study of HCMV in SC. They found that HCMV genomic and protein was present 100% in multiple SC (Cobbs *et al*., 2002). This study result showed that there was no difference between HCMV reactivation and types of cancer. In this study, HCMV prevalence was found as 59.9% and 40.1% in SC and HM respectively. This result was promoted by several studies all over the world. They found that HCMV was detected in different types of cancer such as in BC 92%, sentinel lymph nodes 94%, brain metastases from BC 99% (Taher *et al*., 2014; Rahbar *et al*., 2017), OC 97% (Yin *et al*., 2020) and CRC 90-100% (Melendez & Razonable, 2014; Taher *et al*., 2014). Furthermore, Hunter-Schlichting, demonstrated that HCMV DNAemia was highly prevalent 79% in pleural mesothelioma (Schlichting *et al*., 2021). Although, accurate data that reflected HCMV infection among SC patients in India was published by Agrawal and his group, they reported that HCMV was detected in 41.1% of patients (Agrawal *et al*., 2020). Moreover, Chamseddine reported that HCMV reactivation was 35% among cancer patients in Lebanon (Chamseddine *et al*., 2020). A recent study from Germany found that HCMV

seroprevalence was 61% among oncological patients (Herbein, 2018). Further, HCMV was detected in 95%-100% of BC in Egyptian women (El-Shinawi *et al*., 2016; El Shazly *et al*., 2018), Harkins 2010 in USA was 79% (Harkins *et al*., 2010). In Norway a study by Geisler and his group in 2019 found HCMV is 90% (Geisler *et al*., 2019) and in Iraq 94% (AlNuaimi *et al*., 2018; Salman & Al-Azzawi, 2020). However, Muhsin in 2014 reported lower HCMV prevalence in BC in Iraqi women - 67% (Muhsin, 2014), also 58% in Iranian women 58% (karimi *et al*., 2016). High rate of 76% HCMV pp65 was detected in biopsies of 29 patients with diffuse large B-cell lymphoma of the CNS (Libard *et al*., 2014). Finally HCMV was detected in 77.5% in CC in general population in India (Ghosh *et al*., 2019) and in 53% of CRC in Iran (Mehrabani-Khasraghi *et al*., 2016). Likewise, regarding HCMV in HM there were a lot off studies because HCMV reactivation was less common in ST due to less severe immunosuppression and no experience prolonged periods of neutropenia (Gudiol *et al*., 2016).

This study results showed the prevalence of HCMV in HM was 99.5%. Those results were inconsistent with Loutfy and his colleagues data that found that seroprevalence of HCMV IgG antibody was 100%, all 68 leukemic patients had anti HCMV IgG antibody (Loutfy *et al*., 2006). Further, HCMV was detected 100% in ALL and Acute Myelocytic Leukemia patients in USA (Francis *et al*., 2017). Another study in Brazil by de Melo Silva . in 2021 found that seroprevalence of HCMV IgG in leukemia and lymphoma was 91% and 91.7% respectively (de Melo Silva *et al*., 2021). A novel study was published and demonstrated that HCMV was detected with a 95.28% overall seroprevalence among HM patients in KSA (Zaidi *et al*., 2019). Additionally, in HM another two studies reported that the incidence of HCMV infection was 32%-58% in acute leukemia patients (Chen *et al*., 2010). Further, Piukovics in 2017 reported that HCMV was detected in 75.5% of HM (Piukovics *et al*., 2017). In addition, there were also studies about the association between HCMV infections with HM but the prevalence of HCMV is less than 50% such as, in United Kingdom found that HCMV was 48.5% in HM (Tay *et al*., 2014). Another study in Iran showed that the prevalence of HCMV was 40.1% in HM and the highest incidence was 20.6% and observed in NHL (Mehrabani-Khasraghi *et al*., 2016). Muhsin in Iraq revealed a 28% prevalence of HCMV in ALL patients (Muhsin *et al*., 2014).

Otherwise, a study was carried out by Young Lee and his group in Korea and it demonstrated that HCMV had a 17.9% incidence among HM patients (Lee *et al*., 2017).

This result showed that all the age groups of cancer patients were at the same risk of HCMV reactivation. This result was supported by similar results reported in majority of other studies from Iraq and Egypt. There was no significant difference in the age and HCMV viremia in Iraq and Egypt in all patients (Loutfy *et al*., 2006; Loutfy *et al*., 2017; Al-Toban *et al*., 2018). Also, Han in 2007 reported that higher HCMV antigenemia rates were also associated with older age (Han, 2007). Although, another study in Brazil by de Matos they found that HCMV seroprevalence in HM was 89.4%, which is directly proportional to age of the patient (de Melo Silva *et al*., 2021). The prevalence of HCMV infection observed in this study was similar to that reported in other developing communities but higher than in the developed communities. This may be attributed to the low socio-economic level in Yemen.

Transmission of HCMV infection through blood transfusion was first recognized >59 years ago (Anderson & Larsson, 1963). This study result showed the prevalence of HCMV in cancer patients with history of blood transfusion was 99.5%. These result was supported by several studies carried on the prevalence of HCMV in blood donors such as Zuhair in 2019 HCMV in blood donor was 86%, Eastern Mediterranean Region 92%, African 90%, Western pacific 90% and South East Asia 88% (Zuhair *et al*., 2019). In Egypt high rates of HCMV infections were attributed to the high HCMV seroprevalence among blood donors in Egypt, as reported by Gawad and his group in 2016 found that 96.6% of blood donors were HCMV seropositive (Gawad *et al*., 2016). Many studies from Bangladesh, India, Iran, Iraq, Pakistan, Brazil, Japan, Ghana and Nigeria detected the seroprevalence of HCMV in blood donors varied between 90%-100% (Eivazi *et al*., 2013; Das *et al*., 2014; Khudir & Molan, 2014; Mahmood *et al*., 2014; Safabakhsh *et al*., 2014; Henry *et al*., 2016; Islam Shaheen *et al*., 2020). However, other studies showed a high worldwide seroprevalence for HCMV among blood donors, such as in Nigeria 95.8%, Brazil 96.4%, Turkey 97.2%, Iran 98.5% and the India 98.6% (Das *et al*., 2014), Iraq 97.4% (Mahmood *et al*., 2014). In Yemen a study by AL Saberi in 2018 showed the prevalence rate of HCMV IgG among blood donor was 96.6 % (Al-Sabri *et al*., 2017), which was similar

to previous studies performed in Sana'a 100% (Al-Samawi, 2003) and Hodeidah 98.7% (Alghalibi *et al*., 2016).

In Yemen the risk for TT infection is very high due to not check for HCMV during donation. Without prophylactic treatment approximately 70% of patients would develop a HCMV infection (Ljungman *et al*., 2011). Several studies have suggested that HCMV is an important TT pathogen (de Melo Silva *et al*., 2021). Finally, patients with HM need several transfusions in the admission period and outpatient clinic. Thus, these patients are at great risk of HCMV infection as a result of taking a significant volume of donated blood and undergoing treatments by cytotoxic drugs in Iran (Eivazi *et al*., 2013).

This study has shown that the incidence of HCMV in cancer patients undergoing organ transplantation was 100%. These results promoted by several studies discussed the prevalence of HCMV in transplant patients. However, there is a correlation between incidence of HCMV and type of transplant, the highest incidence seen in lung or heart–lung recipients it was 19% to 75%, in patients undergoing pancreas, 15%-50%, in liver recipients 65%, and in kidney recipients it was 6.2-60%, (Bosch *et al*., 2011; Beam & Razonable, 2012). Although, 91 of 213 42.7% patients developed HCMV viremia after HCT in USA (Huang *et al*., 2016). Further, Zhao and his colleagues in 2017 demonstrated that reactivation of HCMV occurs from latency, or often after SOT and blood transfusion (Zhao *et al*., 2017). Recently, Zuhair in 2019 found that the incidence of HCMV in organ donor was 86% (Zuhair *et al*., 2019). In addition, many studies have shown that to reduce the risk of HCMV infection or reactivation in immunocompromised patients such as under transplantation, cancer patients undergo chemotherapy and steroid therapy, antiviral prophylaxis should be given (Cayatte *et al*., 2013; Britt & Prichard, 2018; Maertens *et al*., 2019). It was reported that reactivation could occur in 25-30% of the patients within three months and within six months with higher positivity if antiviral prophylaxis is not given after transplantation (Osawa & Singh, 2009; Ljungman *et al*., 2011; Watkins *et al*., 2012).

Chemotherapy had many side effects, one of them was markedly suppress cellular immunity and expose patients to a greater risk opportunistic infections such as viral infection including HCMV infection (Boeckh & Nichols, 2004; Kuo *et al*., 2008; Schlick *et al*., 2015; Demirel *et al*., 2021). It

is possible that latent HCMV could subsequently be reactivated by the chemotherapy (Kuo *et al*., 2008). In these studies, we found 85.5% of cancer patients were undergoing chemotherapy and the prevalence of HCMV was 99.5%. These results affirmed by Hatayama and his group who found that HCMV was detected in 67.1% of cancer patients undergoing chemotherapy and steroid therapy in Japan (Hatayama *et al*., 2020). In addition, a recent study in Iraq revealed that there was a little high prevalence 28% of HCMV viremia in Iraqi patients with acute leukemia after chemotherapy (Al-Toban *et al*., 2018). A novel study by Phasuk and his group in 2019 disclosed that the prevalence of HCMV DNAemia was 52% after chemotherapy of pediatric ALL patients (Phasuk *et al*., 2019). Moreover, Bansal from India reported that HCMV infection was found in different regimens of chemotherapy and no special regimen had a particular tendency to HCMV infection. Thus, reactivation of HCMV as a result of immunosuppression by chemotherapy causes a severe clinical manifestation (Bansal & Ghafur, 2020). Further, HCMV reactivation can be life threatening in severity (Cannon *et al*., 2010; Kotton, 2013; Schlick *et al*., 2015; Papazian *et al*., 2016; Schildermans & De Vlieger, 2020). Therefore, reactivation of HCMV was detected because of immunosuppression that develops due to the lymphopenia and dysfunction of lymphocyte. However, this condition was noticed particularly in chemotherapies used in patients with SC also have reported to associate HCMV reactivation (Osawa & Singh, 2009; Beam & Razonable, 2012). On the other hand, some research found a relation between HCMV reactivation and chemotherapy in SC (Kuo *et al*., 2008; Demirel *et al*., 2021).

The result of this study revealed that the seroprevalence of HCMV in cancer patients undergo radiotherapy was 100%. This result was supported by the result of Goerig in 2016 who found that the prevalence of HCMV was 48% in patients with brain cancer after radiotherapy in these patients and 87% required treatment for HCMV associated encephalopathy (Goerig *et al*., 2016).

In this study, there was only 1% of cancer patients taking steroid therapy and the incidence of HCMV was 100%. This result was supported by the result of (Suárez *et al*., 2018). They found that the prevalence of HCMV in patients treated with steroid was 70%, while it was 44% in patients without steroids therapy. Moreover, Marchesi (2018) demonstrated that patients with advanced disease, treated by High-dose steroids, increased the rate of HCMV

infection/ reactivation ranges between 2 and 67% (Marchesi *et al*., 2018). Another study by Xue and his team in 2016 noted that higher corticosteroid doses were correlated with HCMV pneumonia (Xue *et al*., 2016). Further, Tsai (2012) found that high doses of prednisolones increased risk of HCMV infections, (Tsai *et al*., 2012).

This result showed that there was no significant difference in seroprevalence of HCMV reactivation in cancer patients regarding to antiviral prophylactics. Further, when HCMV infection or reactivation confirm in patients receiving chemotherapy, HCMV treatment should apply (Watkins *et al*., 2012; Kotton, 2013). In addition, in HCMV infection the mortality was reduced by accurate diagnosis and rapid treatment (Osawa & Singh, 2009; Linares *et al*., 2011; Watkins *et al*., 2012). Moreover, the incidence of HCMV was lower in liver transplantation patient with preemptive antiviral therapy (Singh *et al*., 2020).

Conclusion:

CMV seroprevalence is very important for national health care. CMV IgG Abs were detected in almost specimens of patients that received chemotherapy. CMV reactivation remains a significant clinical problem in these patients. Since CMV infection and its manifestation in cancer patients is probably underdiagnosed, given the high morbidity and mortality in these patients (with or without co-infections), it is very important to suspect and treat CMV reactivation. This study and other studies showed the of reactivation of CMV and chemotherapy in cancer patients, which makes CMV infection a serious threat for the patients receiving chemotherapy. Since CMV infection and its manifestation in patients with SC is probably underdiagnosed. Given the high morbidity and mortality in these patients (with or without co-infections), it is very important to suspect and treat CMV reactivation.

Recommendations:

This study recommends the following steps to minimize the CMV reactivation among cancer patients:

CMV test should be done as a routine test for all cancer patients undergoing chemotherapy.

Antiviral against CMV must be given to cancer patients receiving chemotherapy if a patient has both clinical features and CMV positivity.

Further, blood bag given to cancer patients undergoing chemotherapy should be taken from seronegative CMV donors.

CMV routine screening test is very important for cancer patients with an observation for the development of any clinical manifestations of CMV infection.

If a patient has both clinical features and CMV positivity, then CMV antiviral prophylaxis may effectively prevent CMV reactivation, manage CMV infection complications and improve CMV infection outcomes.

Ethics approval:

The study was approved by the Faculty of Applied Sciences at Taiz University (No. 851). Permission was obtained from both Al- Amal Center For Treatment Of Oncology Patients. Taiz City and the participants in the study. No personal identifiers were used during samples or data collection; all samples were coded with a distinct research ID.

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