

Seroprevalence Of Cytomegalovirus Among Hemodialysis Patients In Misurata City-Libya

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Abstract Cytomegalovirus (CMV) belongs to the herpes virus family, it has the ability to cause systemic infection and serious diseases in immunocompromised patients such as hemodialysis patients. The aim of this study was to investigate the prevalence of CMV infection among hemodialysis (HD) patients. One hundred and seventy (170) of HD patients (95 males & 75 females) attending the Misurata center for nephrology and dialysis were included in this cross-sectional study, thirty (30) of apparently healthy individuals (13 male & 17 female) were also employed as a control group. Detection of CMV-IgM & CMV-IgG antibodies in serum samples was carried out by Enzyme-Linked Immunosorbent Assay technique. Results showed that CMV-IgM antibodies were detected in 29/200 (14.5%) of the total study population, whereas 21/170 (12.4%) of hemodialysis patients and 8/30 (26.7%) of control subjects were seropositive for CMV IgM antibodies; in addition 186/200 (93%) of the total study population were seropositive for CMV-IgG antibodies, in which 162/170 (95.3%) of HD patients and 24/30 (80%) of the control group were seropositive for CMV IgG antibodies; the seroprevalence of CMV-IgM antibodies was significantly correlated with the frequency of hemodialysis/week, kidney transplantation, blood transfusion, surgical operations, and therapeutic drugs (P= 0.035, 0.039, 0.041, 0.000, and 0.004 respectively); however, seroprevalence of CMV-IgG antibodies was significantly associated with duration of ESRD & HD, and frequency of hemodialysis/week (P= 0.019, 0.020 respectively). In conclusion, results showed a high prevalence of CMV infection among the study population, which could be related to duration of ESRD & HD, blood transfusion, frequency of hemodialysis/week, surgical operations, therapeutic drugs.

Key words: CMV-IgG, CMV-IgM, Cytomegalovirus, ESRD, Hemodialysis .

الانتشار المصلي للفيروس المضخم للخلايا بين مرضى الغسيل الكلوي في مدينة مصراتة-ليبيا

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المخلص يعتبر الفيروس المضخم للخلايا (CMV) هو احد الفيروسات الانتهازية التي تعيش في مضيفها الإنسان، حيث يشكل مشكلة صحية ومخاطر اضافية للمرضى الخاضعين لعملية الغسيل الكلوي. وقد هدفت هذه الدراسة الى تحديد مدى الانتشار المصلي للأجسام المضادة للفيروس (الجلوبيينات المناعية) CMV-IgM و CMV-IgG في مرضى الفشل الكلوي المزمن الخاضعين لعملية الغسيل الكلوي الدموي المترددين على مركز العلاج والغسيل الكلوي بمستشفى مصراتة المركزي. أجريت هذه الدراسة على 170 من المرضى الخاضعين للغسيل الكلوي (95 ذكور، 75 أنثى)، ومقارنتهم مع مجموعة ضابطة تتكون من 30 شخصا من الأشخاص الأصحاء ظاهريا (13 ذكور، 17 أنثى)، وذلك باستخدام تقنية المقايسة المناعية للإنزيم المرتبط (ELISA). أظهرت النتائج أن نسبة ايجابية انتشار الأجسام المضادة CMV-IgM بنسبة (14.5%)، والأجسام المضادة CMV-IgG بنسبة (93%) في مجتمع الدراسة الكلي؛ ومن بين هذه العينات الإيجابية للأجسام CMV-IgM بنسبة (12.4%) و CMV-IgG بنسبة (95.3%) في مجموعة المرضى مقارنة مع المجموعة الضابطة فإن الإيجابية CMV-IgM بنسبة (26.7%)، و CMV-IgG بنسبة (80%) مع وجود فروق معنوية وتأثير ذات دلالة احصائية

وعلاقة طردية بين انتشار الأجسام المضادة CMV-IgM, IgG بين مجموعتي مجتمع الدراسة وأنها غير مُستقلان. وتكون نسبة الإيجابية للأجسام المضادة موزعة كالتالي: CMV-IgM بنسبة (1.5%)، و CMV-IgG بنسبة (80%)، و IgG, CMV-IgM معاً بنسبة (13%).
الكلمات المفتاحية: الغسيل الكلوي الدموي، الفيروس المضخم للخلايا (CMV)، الأجسام المضادة (الجلوبيينات المناعية)، (CMV-IgG) (CMV-IgM)

1- Introduction

Renal failure is defined as an acute or chronic deficiency in kidney function. It occurs when the kidneys are unable to remove waste products, control blood electrolytes, and maintain fluid balance. The alternative treatment for most cases of end stage renal disease (ESRD) is either by dialysis or kidney transplantation. Hemodialysis is the commonest procedure of renal replacement therapy; where the dialysis process is used to remove excess fluids and harmful substances from the body [1]. Like other developing countries, Libya has a relatively high prevalence of dialysis-treated ESRD; it is about 624 per million population (pmp), as a result of several factors, including diabetes, high blood pressure, glomerulonephritis, kidney stones, genetic and environmental factors [2]. The prevalence rate varied by region, however, the total number of patients undergoing hemodialysis at the Misurata center for nephrology and dialysis was around 300 until the end of the year 2017.

With the increase in the number of patients with kidney failure in recent years, and changes in the type and severity of co-morbidities [3], and spread of infection with viral blood diseases in the dialysis units through kidney machines, in addition to their exposure to frequent blood transfusion, patients on hemodialysis becomes a high risk for infection with Cytomegalovirus (CMV) [4]. Cytomegalovirus (CMV) has become a major public health problem and comprises a great threat to the safety of immunocompromised patients including those with renal failure; which may increase the rates of morbidity and mortality among those patients [5]. It has been well documented that patients on hemodialysis have impaired immune system, which may lead to serious complications resulting from different infections and inflammations including CMV infections and where they have observed deficiencies in T-cells and immune response for the virus infection [6]. It has been also observed that hemodialysis patients have increased in the production of inflammatory factors such as Cytokines, Interleukin-6, Tumor necrosis factor (TNF) [7],[8], due to their frequent exposure to the use of dialysis machines, as well as blood transfusions, which makes them more vulnerable to CMV infection [9].

Cytomegalovirus (CMV) belongs to the herpes virus family [10], it is considered one of the most powerful viruses that can live in the human host, and has the ability to remain in the host in the event of latency after the initial infection and for long periods of life [11]. Infection with human cytomegalovirus is widespread throughout the world, where the prevalence rate ranged from 55%

to 90% [12]. The rate of incidence is varying among different communities, where it depends on several factors including age, sex, ethnicity, population density, socio-economic conditions [13], modes of transmission, personal immunity, chronic diseases, chemotherapy [14], frequency of blood transfusion, as well as time and duration of dialyzing [15].

Cytomegalovirus (CMV) is an opportunistic microorganism, it causes systemic infection and serious diseases in immunocompromised patients [16]. The pathogenicity of the virus is limited in healthy people, and usually not associated with any clinical manifestations, but if the symptoms appear, they are similar to the symptoms resulting from mononucleosis syndrome, which may include: idiopathic fever, loss of appetite with nausea, joint and muscle pain, lymphocytosis, disturbance of liver enzymes, which may last for several weeks and may be associated with other abnormal symptoms such as Meningoencephalitis, Hemolytic anemia, Thrombocytopenia [17],[18]. However, the reactivation of the latent virus is usually associated with a person's immune status, whereas in immunocompromised patients such as the elderly, cancer patients, ESRD patients and organs transplant recipients [5] may cause severe complications [19].

Through reviewing previous studies conducted in several countries around the world, it was observed that the seroprevalence of CMV-IgM and CMV-IgG antibodies in hemodialysis patients have a range of 0-10% and 90-100% respectively [4],[20],[21]. It was also noted that the seroprevalence of CMV-IgG antibodies among blood donors ranged between 74-95% which indicates the risk of transmission of CMV infection following blood transfusion processes [22],[23],[24],[25]. Other studies also reported the occurrence of CMV infection in %60-20 of renal transplant recipients [26],[27]. One study indicated that the seroprevalence of CMV-IgM and CMV-IgG antibodies among renal transplant recipients was 6% and 98%, respectively [21], which makes it one of the main causes for increasing morbidity and mortality for those patients. Some other studies indicated an association and a direct relationship between high blood pressure within the ventricle of the heart and the presence of chronic inflammation in patients with ESRD [28], especially in those with seropositive CMV infection [29].

It is obvious that CMV infection constitutes an additional risk and health problem for hemodialysis patients at the local and national levels, thus the aim of this study was to

investigate the prevalence of CMV infection among ESRD patients undergoing hemodialysis at the Misurata center for nephrology and dialysis.

2-Patients and Methods

Study design: This cross-sectional study was conducted on 170 hemodialysis (HD) patients (95 males & 75 females), out of 300 ESRD patients attending the Misurata center for nephrology and dialysis during the period of February to May 2017. Thirty (30) apparently healthy individuals (13 male & 17 female) were employed as a control group. The age ranges from 10 to 80 years old.

Data collection: A questionnaire was formulated and used to gather personal, clinical and geographical information about each participant. Data was collected by interviewing each participant and inspecting medical records to assure validity of data. Permission to carry out the study was approved by both the Academy of Graduate Studies Misurata-Branch, and Misurata Center for Nephrology and Dialysis.

Samples and methods: Venous blood samples (5 ml) were collected from each participant in a clean sterile test tubes free of any anti-coagulant, then processed to obtain serum for serological tests. Samples were tested for the presence of CMV-IgM & CMV-IgG antibodies by Enzyme-Linked Immunosorbent Assay (ELISA) commercial kit, in accordance with the manufacturer's instructions (Biochek, nc.323vintage, USA), using Microwell reader (Biotek, ELx800 microplate reader, USA) at the wavelength of 450 nm [30].

Statistical analysis: Data was statistically analyzed by Statistical Package for Social Sciences program (SPSS, version 17.0., Chicago, IL, USA). A Chi-Square test was used to compare frequencies and to measure the strength and variety of correlation between different variables. P values <0.05 were considered statistically significant.

3-Results and Discussion

3-1 Results

To the best of our knowledge this is the first study aimed to investigate the prevalence of CMV infection among patients undergoing hemodialysis in Misurata City-Libya. This cross-sectional study was conducted on 170 of HD patients (95 males & 75 females) attending the Misurata center for nephrology and dialysis, out of about 300 ESRD patients (170 males 140 females) attending the center, during the period of February to May 2017. The study also included 30 healthy individuals (13 male & 17 female) as a control group. The ages ranged from 10 to 80 years old. It is noteworthy that 10 patients died while conducting this study.

Seroprevalence of CMV-IgM and CMV-IgG antibodies in the study population

The results shown in Table 1 and figure 1 indicated that the seroprevalence of CMV-IgM antibodies among the total study population (200 samples) were as follows: CMV-IgM antibodies were detected in 29/200 (14.5%) of the total study population. Whereas 21/170 (12.4%) of hemodialysis patients and 8/30 (26.7%) of control

subjects were seropositive for CMV IgM antibodies. On the other hand, 149/170 (87.6%) of hemodialysis patients and 22/30 (73.3%) of the control subjects were seronegative for CMV-IgM antibodies. Results showed statistical significant differences between the patients and the control groups ($P = 0.04$), and a weak positive correlation between the seroprevalence rate of anti-CMV IgM and the study population ($\chi^2 = 0.144$).

Results presented in Table 1 and figure 2 also showed that 186/200 (93%) of the total study population were seropositive for CMV-IgG antibodies; however, out of 170 HD patients, 162 (95.3%) were seropositive and 8 (4.7%) were seronegative for CMV-IgG antibodies. On the other hand, out of 30 control individuals, 24 (80%) were seropositive and 6 (20%) were seronegative for CMV-IgG antibodies. Results also showed statistical significant differences between the patients and the control groups ($P = 0.002$), and moderate positive correlation between the seroprevalence rate of anti-CMV IgG and the study population ($\chi^2 = 0.209$).

As shown in table 2 and figure 3, the distribution of seropositivity for CMV-IgM and CMV-IgG antibodies among the total study population revealed that 13% (26/200), 3/200 (1.5%), and 160/200 (80%) were seropositive for both CMV-IgM & CMV-IgG, only for CMV-IgM, and only for CMV-IgG antibodies respectively. In HD patients group, 19/170 (11.2%) were seropositive for both CMV-IgM & CMV-IgG; however, 2/170 (1.17%) were only seropositive for CMV-IgM, and 143/170 (84.12%) were only seropositive for CMV-IgG antibodies. In the control group 7/30 (23.3%) were seropositive for both CMV-IgM & CMV-IgG; whereas, 1/30 (3.33%) were only seropositive for CMV-IgM, and 17/30 (56.67%) were only seropositive for CMV-IgG antibodies.

Relationship between the seroprevalence of CMV-IgM, CMV-IgG antibodies and some clinical characteristics

Results shown in table 3 indicated that the seroprevalence rate of CMV-IgM antibodies was significantly correlated with the frequency of hemodialysis/week, kidney transplantation, blood transfusion, surgical operations, and therapeutic drugs ($P = 0.035, 0.039, 0.041, 0.000, \text{ and } 0.004$ respectively), as measured by Chi square test. However, there was no correlation between the seroprevalence rate of CMV-IgM antibodies and each of the duration of ESRD & HD, dialyzing time /one stay, clinical symptoms, chronic diseases, systolic blood pressure, diastolic blood pressure, and body mass level ($P = 0.091, 0.867, 0.840, 0.626, 0.606, 0.954, \text{ and } 0.290$ respectively), according to Chi square test. As shown also in Table 3, the seroprevalence rate of CMV-IgG antibodies is significantly associated with the duration of ESRD & HD, and frequency of hemodialysis/week ($P = 0.019, 0.020$ respectively), as tested with Chi square test. Whereas there was no association between the seroprevalence rate of CMV-IgG antibodies and each of the dialyzing time/one stay, kidney transplantation, blood transfusion, surgical

operations, therapeutic drugs, clinical symptoms, chronic diseases, systolic blood pressure, diastolic blood pressure, and body mass level (P= 0.945, 0.922, 0.921, 0.936, 0.947, 0.585, 1.000, 0.330, 0.213, and 0.328 respectively) as evaluated by Chi square test.

3-2 Discussion

The present study showed that 12.4% and 26.7% of the HD patients and control individuals respectively were seropositive for CMV-IgM antibodies, which indicates the existence of primary recent or recurrent infection with cytomegalovirus. Control individuals showed

almost two times higher seropositivity for CMV-IgM antibodies than HD patients. On the other hand, 95.3% of HD patients and 80% of the control subjects were seropositive for CMV-IgG antibodies indicating previous exposure to CMV infection. Recurrent CMV infection was developed in 11.2% of HD patients compared to 23.3% of the control subjects, however, primary recent CMV infection was demonstrated in 1.17% and 3.33% of the

Table 1: Seroprevalence of CMV-IgM and CMV-IgG Antibodies in the Study Population; data are expressed in percentage value (%).

Study population Number(%)	CMV-IgM antibodies		CMV-IgG antibodies	
	positive P	negative N	positive P	negative N
Patients group	170 (85%)	21 (12.4%)	149 (87.6%)	162 (95.3%)
Control group	30 (15%)	8 (26.7%)	22 (73.3%)	24 (80%)
Total	200 (100%)	29 (14.5%)	171 (85.5%)	186 (93%)
P Value		0.04*		0.002*

*P value < 0.05, statistically significant

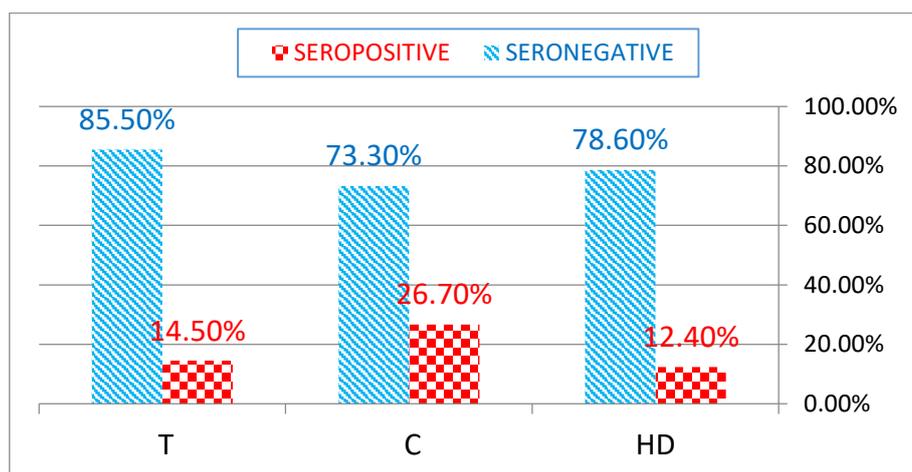


Fig. 1: Seroprevalence of CMV-IgM antibodies in the study population (T: total; C: control; HD: hemodialysis patients).

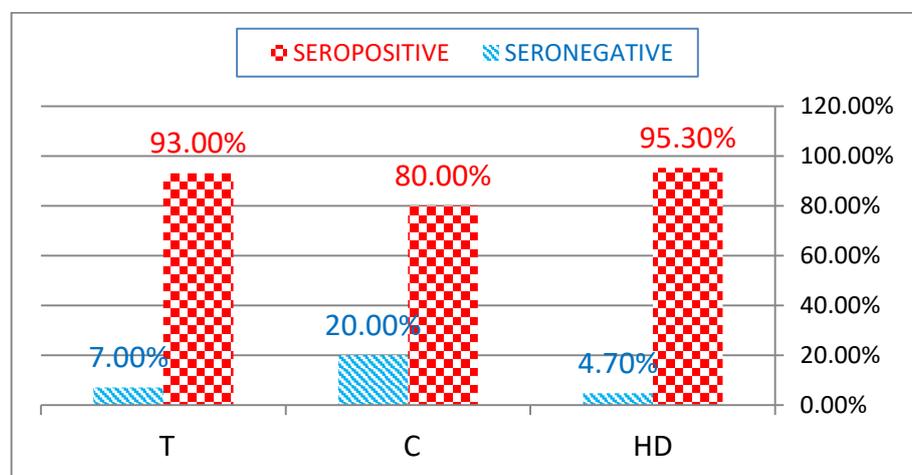


Fig. 2: Seroprevalence of CMV-IgG antibodies in the study population (T: total; C: control; HD: hemodialysis patients).

Table 2: Seropositivity for CMV-IgM and CMV-IgG antibodies in the study population; data are expressed in percentage value (%).

Study population	Number(%)	Seropositive for CMV-IgM (only)	Seropositive for CMV-IgG (only)	Seropositive for CMV-IgM & IgG
Patients group	170 (85%)	2 (1.2%)	143 (84.1%)	19 (11.2%)
Control group	30 (15%)	1 (3.3%)	17 (56.7%)	7 (23.3%)
Total	200 (100%)	3 (1.5%)	160 (80%)	26 (13%)

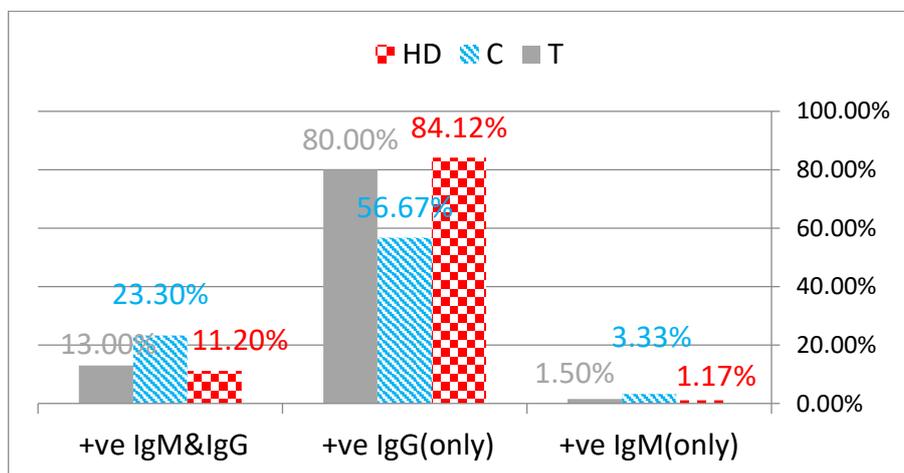


Fig. 3: Seropositivity for CMV-IgM, and CMV-IgG in the study population (HD: hemodialysis patients; C: control; T: total).

Table 3: Relationship Between the Seroprevalence of CMV-IgM, CMV-IgG Antibodies and Some Clinical Characteristics.

Variable	Chi square; p value	
	CMV-IgM	CMV-IgG
Duration of ESRD & HD	0.091	*0.019
Frequency of hemodialysis / week	* 0.035	* 0.020
Dialyzing time /one stay	0.867	0.945
kidney transplantation	*0.039	0.922
Blood transfusion	*0.041	0.921
Surgical operations	*0.000	0.936
Therapeutic drugs	*0.004	0.947
Clinical symptoms	0.840	0.585
Chronic diseases	0.626	1,000
Systolic blood pressure	0.606	0.330
Diastolic blood pressure	0.954	0.213
Body mass levels	0.290	0.328

*p value < 0.05, statistically significant

HD patients and control participants. In addition, 84.12% and 56.67% of HD patients and healthy controls were exposed to past CMV infection. The seropositivity of CMV-IgG antibodies was significantly higher among HD patients compared to the control group. Although the seroprevalence rate of CMV-IgG recorded in this study is within the range that reported by most of the similar previous studies, the seroprevalence rate of CMV-IgM antibodies is obviously higher than that reported in several develop countries. Similar local study conducted in Derna City-Libya showed that 10% and 100% of the HD patients were seropositive for CMV-IgM and CMV-IgG respectively, due to repeated blood transfusion [20]. In Croatia, the seroprevalence rate of CMV-IgM antibodies among HD patients and healthy control subjects were 1.9% and 2.5% respectively, and that of CMV-IgG were 90.7% and 81.9% respectively [31]. Two years later the same authors reported in different study that 91.4% of

the HD patients were seropositive for CMV-IgG antibodies [32].

In a study conducted in Iraq, out of 91 HD patients, 87(95.6%) were seropositive for CMV-IgG antibodies. They concluded that the high seroprevalence rate of CMV among those HD patients was due to their taking of therapeutic drugs, which exposes them to the risk of CMV infection [33]. Whereas in another study carried out in Iraq on 116 of HD patients, 10(8.6%) and 102(87.8%) were seropositive for CMV-IgM and CMV-IgG antibodies respectively [11]. Similarly in Brazil, the seroprevalence rates of CMV-IgM and CMV-IgG antibodies among HD patients were 4.9% and 96% respectively, with a high morbidity rate for that study population [34]. A study conducted in Iran on 84 HD patients reported that 6(7.1%) and 65(77.4%) were seropositive for CMV-IgM and CMV-IgG respectively [35]. Egyptian study carried out by Abu-Elyazed and others using ELISA technique to investigate the

prevalence of CMV infection among HD patients showed seropositivity of 11% and 98% of the patients for CMV-IgM and CMV-IgG antibodies respectively [36]. In Turkey, a study conducted using also ELISA technique indicated that only 0.5% of the HD patients were seropositive for CMV-IgM antibodies, (which is not in congruence with our results), however 99.5% were seropositive for CMV-IgG antibodies; the study also showed a direct correlation between the seroprevalence of CMV-IgG antibodies and the study population, but absence of any association between the seroprevalence of CMV-IgM antibodies and the study population [7].

In Sudan, almost similar results were obtained from two separate studies, in which 95% [37] and 95.7% [38] of HD patients were seropositive for CMV-IgG antibodies. In another study, carried out in Morocco, CMV-IgM antibodies were detected in 6.9% and 6.7% of HD patients and control subjects respectively, however CMV-IgG antibodies were detected in 100% and 90% of HD patients and control subjects respectively [39].

Although results of this study showed higher CMV-IgM rate than that reported by most of the similar studies from different countries, CMV-IgG seroprevalence rate was in line with that reported by most of the previous studies. Compared to this study, however, some studies showed different results; For example, high seroprevalence rate of CMV-IgM antibodies among HD patients were reported from Sudan (45.2%) [38] and from Iran (20%) [40]. Low seroprevalence rate of CMV-IgG were also reported from Iran (34.4%) [40], and from Saudi Arabia (61.1%) [22]. Differences in results could be attributed to some factors such as general public health status, nosocomial infection, socio-economic status, regional & environmental factors, and assay methods.

Results reported herein showed that the incidence of primary infection or reactivation of latent virus (as indicated by detection CMV-IgM antibodies) is significantly correlated with the frequency of hemodialysis/week, kidney transplantation, blood transfusion, surgical operations, and therapeutic drugs. However, past exposure to CMV infection (as indicated by detection of CMV-IgG antibodies) was shown to be significantly correlated with the duration of ESRD & HD, and frequency of hemodialysis/week. These findings are in agreement with some similar studies. Seroprevalence rates of CMV-IgM antibodies were found to be significantly associated with frequency of hemodialysis/week [15], and blood transfusion [15],[20],[41]. Significant correlation between the seroprevalence rate of CMV-IgG antibodies and duration of ESRD & HD, frequency of hemodialysis/week were also reported [15]. In addition, some studies showed no association between the seroprevalence rate of CMV-IgM antibodies and the duration of ESRD & HD [20],[35],[40], blood transfusions, surgical operations [23], clinical symptoms [20], systolic & diastolic blood pressure, body mass levels [42]. Also, there were no significant correlation between the seroprevalence rate of CMV-IgG antibodies and duration of ESRD & HD [40], blood

transfusions [23],[24], surgical surgeries [23], Chronic diseases (such as blood pressure and diabetes) [43], systolic and diastolic blood pressure, and body mass levels [42].

On the contrary, some other studies have shown different results compared to our findings. For example, some studies have shown that there was no significant correlation between the seroprevalence of CMV-IgM antibodies and the duration of ESRD & HD, therapeutic drugs [44], frequency of hemodialysis/week [35]. In addition, there was no significant correlation between the seroprevalence rate of CMV-IgG and duration of ESRD & HD [7],[33],[40],[44], frequency of hemodialysis/week [35],[40], therapeutic drugs [44], while one other study showed significant correlation between the seroprevalence rate of CMV-IgG and blood transfusion for HD patients [41].

4- Conclusion

Results reported herein showed a high prevalence of CMV infection among the study population at the Misurata Center for Nephrology and Dialysis, which could be related to some clinical characteristics such as blood transfusion, duration of ESRD & HD, frequency of hemodialysis/week, surgical operations, therapeutic drugs, nosocomial infection and also to some socio-economic and environmental factors. High CMV seropositivity is a threat to safety of HD patients which may lead to increase morbidity and mortality among them.

Recommendation: Screening tests result for CMV infection should be included as a routine screening protocol in all hemodialysis centers. Similar screening should be strictly implemented to all blood banks prior to blood donations so as to prevent the transmission of CMV.

Dissemination of information on the results of this study should be conducted to all hemodialysis centers to promote awareness on the prevalence of this infection so that counter measures can be formulated by different health care agencies to prevent the spread of this virus among hemodialysis patients.

Population education on the mode of transmission of CMV should also be given priority as indicated by a very high seroprevalence among healthy individuals used as control group

Abbreviations

CMV: Cytomegalovirus; ESRD: End stage renal disease; HD: Hemodialysis

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