

Original Article

Risk factors and outcomes of cytomegalovirus infection in the intensive care unitMohamad Ali Tfaily¹, Joe-David Azzo^{2#}, Amal Gharamti^{3#}, Marwan Ghanem², Rayyan Wazzi-Mkahal⁴, Zeina A Kanafani²¹ Emory University, Atlanta, GA, United States² American University of Beirut, Beirut, Lebanon³ Yale University, New Haven, CT, United States⁴ American University of Beirut Medical Center, Beirut, Lebanon

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Abstract

Introduction: Cytomegalovirus (CMV) infection has long been recognized as an important viral syndrome in the immunocompromised host. The disease is less well described in critically-ill patients. We evaluated the risk factors for the development of CMV infection in patients admitted to the intensive care unit (ICU). We also compared the outcomes of CMV infection in ICU patients to those of patients with hematological malignancies.

Methodology: This is a retrospective study composed of three arms: patients admitted to the ICU with infection (ICU + / CMV + arm), patients admitted to the ICU who did not develop CMV infection (ICU + / CMV- arm, and patients with hematological malignancies on the hematology ward without CMV infection (ICU - / CMV + arm).

Results: Patients who were admitted to ICU for surgical causes had a decreased risk of CMV infection. On the other hand, receiving corticosteroids and vasoactive drugs was associated with an increased risk of CMV infection with adjusted odds ratios (aOR) of 2.4 and 25.3, respectively. Mortality was higher in ICU + / CMV + patients compared to ICU - / CMV + patients. In the ICU + / CMV + population, male sex and being on mechanical ventilation after CMV infection were independent predictors of mortality (aOR 4.6 and 5.0, respectively).

Conclusions: CMV infection in ICU patients is a potentially serious disease requiring close attention. The findings from our study help in identifying patients in the ICU at risk for CMV infection, thereby warranting frequent screening. Patients at high risk of death (male, on mechanical ventilation) should receive prompt treatment and intensive follow-up.

Key words: CMV; critical care; immunocompromised; risk factors; outcomes.*J Infect Dev Ctries* 2024; 18(4):565-570. doi:10.3855/jidc.17853

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Copyright © 2024 Tfaily *et al.* This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.**Introduction**

Cytomegalovirus (CMV) is a well-recognized pathogen worldwide with a global and Eastern Mediterranean prevalence of 83% and 90%, respectively [1]. While the acute infection in the host with intact immunity is self-limited and often mild, viral infection in the immunocompromised patient population is a traditional challenge given its potentially severe manifestations [1,2]. However, CMV infection is garnering increasing interest in patients admitted to the intensive care unit (ICU) as its role in this population is now being better acknowledged and understood [3].

CMV disease can present with a myriad of different symptoms in immunocompetent adults, resulting in delayed diagnosis, adverse health outcomes, and an increased financial burden [4]. CMV infection and

infection are estimated to occur in 27% and 31% of ICU patients, respectively [5]. Several factors can influence the incidence of infection including the etiology of the critical illness, the site of testing, and the timing of testing [6-8]. It has been previously questioned whether CMV is a bystander or an actual pathogen in ICU patients [9]. There is evidence to suggest, however, that CMV infection and infection in the critically ill patient population is associated with an increase in all-cause mortality, hospital stay, and duration of mechanical ventilation [5,10]. Screening guidelines for CMV infections in critically ill patients are still not well established, but experts recommend it in certain settings such as sepsis, burns, trauma, and ICU-acquired pneumonia, especially in mechanically ventilated patients [6]. Antiviral agents available for prophylaxis and treatment of CMV include ganciclovir, foscarnet,

and cidofovir, but each is associated with potentially severe adverse effects. Pre-emptive CMV treatment and prophylaxis have been studied extensively in the immunocompromised population and are effective in reducing the risk of CMV disease and all-cause mortality [11]. Such strong evidence is lacking in immunocompetent critically ill patients with CMV infection.

The purpose of this study is to identify the risk factors for CMV infection in ICU patients and to compare the outcome of CMV infection in ICU patients to that in patients with hematologic malignancies.

Methodology

Study setting

The population of the study consists of patients who were admitted to the American University of Beirut Medical Center (AUBMC) between January 2005 and December 2018. AUBMC is a teaching hospital in Lebanon with a medical-surgical-neuro-ICU unit and a hematological malignancy unit providing tertiary care to a large proportion of the Lebanese population.

Study population

Cases consisted of patients who had a positive blood CMV PCR of more than 700 copies/mL in the setting of a critical illness that required admission to the ICU (ICU + / CMV + group). The ICU control group consisted of patients admitted to the ICU during the same period as the cases, and who had a negative screening test for CMV infection (ICU + / CMV - group). The hematological controls were patients with hematological malignancies admitted during the same period as the cases, and who had a positive screening test for CMV infection (ICU - / CMV + group). Patients less than 18 years of age, known or suspected HIV infection, or solid organ transplant recipients were excluded from the study.

Data collection

Patient-specific clinical and laboratory data were collected retrospectively from patients' medical records

using a detailed case report form. Each patient was included in the study only once based on the first CMV viremia event during the study period.

Data analysis

Data analysis was performed using IBM® SPSS® v28.0. Descriptive statistics were obtained for the variables and outcomes involved. Bivariable analysis was performed using Chi-square for categorical variables and independent Student's T-test for continuous variables to determine unadjusted odds ratios (uOR) and 95% confidence intervals (CI). Variables with a *p* value < 0.2 on bivariable analysis were included in the multivariable logistic regression model, which was performed using the Forward Likelihood Ratio (LR) method on SPSS® to determine adjusted odds ratios (aOR) and 95% CI.

Ethical considerations

This study was approved by the Institutional Review Board (IRB) of the American University of Beirut. Once data collection was complete, all patient identifiers were removed from the final database.

Results

A total of 275 patients were included in the study, 61 in the ICU + / CMV + group, 133 in the ICU + / CMV - group, and 81 in the ICU - / CMV + group. The characteristics of the patients in each arm of the study are presented in Table 1. The average age varied between 58 years in the ICU - / CMV + arm to 67 years in the ICU + / CMV + group. Hypertension was more common in the ICU + / CMV + group while immunosuppression and receipt of anti-CMV prophylaxis were more common in the ICU - / CMV + group.

Risk factors for the development of CMV infection were assessed by comparing the ICU + / CMV + group to the ICU + / CMV- group (Table 2). The use of vasoactive drugs before CMV infection was associated with the highest risk for CMV infection (aOR = 25.3; 95% CI 8.8-73.0) followed by steroid use in the past 30

Table 1. Descriptive statistics of patients in each group of the study.

Variable	ICU+/CMV+ group, (N = 61)	ICU+/CMV- group, (N = 133)	ICU-/CMV+ group, (N = 81)
Age, years	67 ± 15	61 ± 19	58 ± 17
Gender	37 (60.7)	82 (61.7)	50 (61.7)
Diabetes	19 (31.1)	45 (33.8)	16 (19.8)
Hypertension	37 (60.7)	64 (48.1)	24 (29.6)
Steroids	30 (49.2)	49 (36.8)	27 (33.3)
Immunosuppression	10 (16.4)	21 (15.8)	81 (100)
Anti-CMV prophylaxis	1 (1.6)	10 (7.5)	19 (23.8)
Time to screening, days	19 ± 26	11 ± 10	13 ± 14

Numbers represent no. of patients (%) for categorical variables and mean ± SD for continuous variables. ICU: intensive care unit; CMV: cytomegalovirus; SD: standard deviation.

days (aOR = 2.4; 95% CI 1.1-5.5). Time to CMV screening increased the risk of CMV infection, with a risk increase of 10% for every delay of one day (aOR = 1.1; 95% CI 1.0-1.1). Having a surgical cause of ICU admission decreased the risk of development of CMV viremia compared to having a medical cause (aOR 0.1; 95% CI 0.02-0.2). Receiving anti-CMV prophylaxis in the past seven days was protective against CMV infection, although the association did not reach statistical significance.

The outcomes of patients with CMV infection (ICU + / CMV + group vs. ICU- / CMV + group) are displayed in Table 3. ICU patients were more likely to develop a bacterial hospital-acquired infection, acute kidney injury, and ventilator-associated pneumonia after CMV infection than time non-ICU patients. Mortality after CMV infection was higher in ICU patients (59.0% vs. 32.1%; $p = 0.001$). The strongest predictor for mortality in all patients with CMV infection (ICU + /CMV + and ICU - / CMV + groups) was mechanical ventilation after CMV infection (aOR

7.5; 95% CI 3.0-18.7) (Table 4). Other independent predictors were the use of vasoactive drugs before CMV infection (aOR 3.4, 95% CI 1.4-8.3) and male sex (aOR 2.8, 95% CI 1.1-7.0). It is noteworthy that receiving treatment for CMV did not improve survival. When considering only the ICU + / CMV + population, the only independent risk factors for mortality were mechanical ventilation after CMV infection (OR 5.0, 95% CI 1.4-17.9) and male sex (aOR 4.6, 95% CI 1.3-16.8) (Table 5).

Discussion

Given the lack of clear-cut evidence on CMV screening and prophylaxis in critically ill patients, the delineation of risk factors is crucial for a better understanding of the epidemiology of CMV disease in the ICU population, which would pave the way to the conduct of clinical trials that can further address this topic [8]. In this study, we determined the risk factors for developing CMV in a population of ICU patients at a tertiary care center in Lebanon. We also compared the

Table 2. Bivariable and multivariable analysis showing the risk factors for the development of CMV infection among patients in the ICU (ICU+/CMV+ group vs. ICU+/CMV- group).

Variable	uOR (95% CI)	aOR (95% CI)	p value
Vasoactive drugs prior to CMV reactivation	13.1 (5.9-29.0)	25.3 (8.8-73.0)	< 0.001
Corticosteroid use in the past 30 days	1.7 (0.9-3.1)	2.4 (1.1-5.5)	0.04
Time to CMV screening	1.0 (1.0-1.1)	1.1 (1.0-1.1)	0.001
Surgical reason for ICU admission	0.2 (0.1-0.5)	0.1 (0.02-0.2)	< 0.001
Heart failure	2.6 (1.2-5.7)	NS	NS
Anti-CMV prophylaxis	0.2 (0.03-1.6)	NS	NS

ICU: intensive care unit; CMV: cytomegalovirus; uOR: unadjusted odds ratio; aOR: adjusted odds ratio; CI: confidence interval; NS: not significant.

Table 3. Outcomes of patients with CMV reactivation stratified by ICU status (ICU+/CMV+ group vs. ICU-/CMV+ group).

Variable	ICU patients, (N = 61)	Non-ICU patients, (N = 81)	p value
Hospital-acquired infection	35 (57.4)	27 (33.3)	0.004
Acute kidney injury	29 (47.5)	26 (32.1)	0.05
Ventilator-associated pneumonia	18 (29.5)	7 (8.6)	0.001
Death	36 (59.0)	26 (32.1)	0.001

ICU: intensive care unit; CMV: cytomegalovirus. Numbers represent no. of patients (%).

Table 4. Bivariable and multivariable analysis of risk factors for death among all patients with CMV reactivation (ICU+/CMV+ group and ICU-/CMV+ group).

Variable	uOR (95% CI)	aOR (95% CI)	p value
MV after CMV reactivation	7.5 (3.4-16.6)	7.5 (3.0-18.7)	< 0.001
Vasoactive drugs prior to CMV reactivation	5.4 (2.5-11.5)	3.4 (1.4-8.3)	0.01
Male sex	2.4 (1.2-4.9)	2.8 (1.1-7.0)	0.03
Treatment for CMV	0.7 (0.3-1.4)	NS	NS

ICU: intensive care unit; CMV: cytomegalovirus; uOR: unadjusted odds ratio; aOR: adjusted odds ratio; CI: confidence interval; MV: mechanical ventilation; NS: not significant.

Table 5. Bivariable and multivariable analysis of risk factors for death among patients with CMV reactivation in the ICU (ICU+/CMV+ group).

Variable	uOR (95% CI)	aOR (95% CI)	p value
MV after CMV reactivation	4.3 (1.4-12.6)	5.0 (1.4-17.9)	0.02
Male sex	3.3 (1.1-9.7)	4.6 (1.3-16.8)	0.02

ICU: intensive care unit; CMV: cytomegalovirus; uOR: unadjusted odds ratio; aOR: adjusted odds ratio; CI: confidence interval; MV: mechanical ventilation.

outcomes of CMV infection in ICU patients and in patients with hematological malignancies and evaluated risk factors for mortality.

We found that the use of vasoactive drugs, intake of steroids within 30 days, and having a medical reason for ICU admission all increased the risk of CMV infection. This is compatible with the existing literature [12]. A longer time for CMV screening added a small but significant risk for infection due to delayed detection, further delineating the importance of early identification of patients who are at higher risk of infection. Time to CMV screening can be considered as a surrogate marker for length of hospital stay prior to CMV infection and has been previously demonstrated in the literature [10, 13]. It is worth noting that receiving anti-CMV prophylaxis was not associated with decreased odds of CMV infection in our study. One clinical trial assessing the efficacy of ganciclovir prophylaxis found no significant difference in mortality, length of ICU stay, or incidence of secondary bacteremia or fungemia [14]. Part of the challenge in establishing clear-cut CMV prophylactic guidelines includes the discouraging safety profiles of anti-CMV drugs on the kidney and bone marrow. This is of particular concern in critically ill patients who often have organ dysfunction, and where the use of anti-CMV prophylaxis would place these patients at an added risk for further dysfunctions and secondary infections [13]. Although kidney disease was dropped from our multivariable model, renal failure was found to be associated with CMV infection in a study by Jaber *et al.* [15]. In addition, while longer exposure to mechanical ventilation is another well-established risk factor for CMV infection, it was not statistically significant in our study [13]. This might be explained by a lack of sufficient power, especially in the presence of the use of vasoactive drugs prior to CMV infection, which can be an effect modifier in the interaction of intubation and CMV infection, since the use of vasoactive substances is a well-known risk factor for mechanical ventilation [16].

Upon comparing the outcomes of CMV infection in ICU patients and patients with hematological malignancies, we found that the ICU population was more likely to develop bacterial hospital-acquired infections overall, acute kidney injury, and ventilator-associated pneumonia following CMV infection. These are expected findings and are also supported by the literature, which shows an increase in the incidence of nosocomial infections, in particular ventilator-acquired pneumonias and fungal infections, in ICU patients with CMV infection [17]. Evidence suggests that lung

involvement plays an important role in the pathogenicity of CMV due to it being a major site of CMV latency and infection [17]. After infection, CMV infection can result in the release of pulmonary interleukins and cytokines which can precipitate the development of ARDS. This could potentially explain the higher incidence of nosocomial pulmonary infections [17]. Although overall in-hospital mortality following CMV infection was higher in critically ill patients than in patients with hematological malignancies, mortality attributable to CMV is more difficult to determine given the complexity of ICU patients and their inherent higher risk of death in the short term. A meta-analysis by Kahil *et al.* showed that active CMV infection in ICU patients is associated with an 81% increase in risk of death compared to ICU patients without CMV infection [18]. We were not able to identify any studies directly comparing the mortality rates in ICU patients and patients with hematological malignancies.

Regarding risk factors for mortality following CMV infection, we found higher odds of death in males and in patients who were intubated following their CMV infection. Receipt of vasoactive drugs prior to CMV infection was significant only in the model that included ICU and non-ICU patients, but not among ICU patients exclusively. Several hypotheses have been suggested to explain the increased mortality in males following CMV infection, including early onset immunosenescence [19]. Accelerated immune aging in males can be associated with the increased mortality of CMV infection in this population [19]. In addition, males with CMV infection have a lower CD4/CD8 ratio. This could be the result of either a decreased cell generation from precursor cells or an increased turnover of T-cells towards more exhausted effector memory cell types. The latter would impair the capacity to develop memory immunity towards other pathogens, increasing susceptibility to infections and death [19]. This reduction in CD4 and CD8 T cells was not shown in females of middle age, and differences between CMV + and CMV- females may become more apparent beyond the age of 65 [19]. The association between mechanical ventilation and poor outcomes is compatible with findings from other studies [20]. In a matched cohort study, patients with CMV stayed on mechanical ventilation for a longer duration than non-CMV patients (35 ± 27 vs. 24 ± 20 days, respectively; $p = 0.03$) [15]. In another study, the number of ventilator-free days was reduced from a median of 34 days to a median of 0 days upon development of CMV infection [21]. Anti-CMV therapy did not improve

patient survival in our ICU population. However, treatment is still recommended in high-risk patients with viral loads of > 500 IU/mL and evidence of lung involvement [20]. According to Papazian *et al.*, risk factors warranting treatment include 2 or more of the following: leukopenia, hemophagocytosis, absence of a bacterial agent, mechanical ventilation for more than 2 weeks, elevated liver enzymes, elevated bilirubin, fever, and diarrhea [20]. In the absence of clinical signs of infection, pre-emptive CMV therapy is recommended with increasing trends in viral load and when the risk-benefit ratio is favorable [22].

Despite being the first study to describe CMV infection in ICU patients from the Middle East and North Africa region, our study has obvious limitations, including the retrospective nature and the small sample size.

Conclusions

We were able to identify risk factors and outcomes associated with CMV infection in the critically ill population. We believe this study adds to the existing knowledge in attempting to identify patients at the highest risk for CMV infection and mortality. Our findings highlight the need for clear treatment and prophylaxis guidelines in immunocompetent patients who become critically ill.

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Ethics approval

This retrospective case-control and cohort study chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of the American University of Beirut approved this study.

Availability of data and material

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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