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María Jesús Pérez-Granda[1,2,3]
Pilar Catalán[1]
Patricia Muñoz[1,2,3,7]
Teresa Aldámiz[1]
Juan Camilo Barrios[4]
Carlos Ramírez[4]
Rita García-Martínez[5]
María Victoria Villalba[5]
Luis Puente[6]
Emilio Bouza[1,2,3,7]

Cytomegalovirus reactivation in patients diagnosed with severe COVID-19: A point prevalence study in a general hospital

[1]Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]CIBER de Enfermedades Respiratorias-CIBERES (CB06/06/0058), Madrid, Spain
[3]Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain
[4]Department of Critical Care, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[5]Department of Internal Medicine, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[6]Department of Pneumology, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[7]Medicine Department, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

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ABSTRACT

Purpose. To determine the prevalence of CMV reactivation in a population admitted for severe COVID-19 to a general hospital.

Methods. Point prevalence study in all hospitalized patients with severe COVID-19 (admitted either to general wards or ICU). Determination of the presence of CMV DNA in circulating blood. COVID-19 was confirmed in patients with compatible clinical manifestations, usually with pneumonia and a positive nasopharyngeal PCR test.

Results. We included 140 hospitalized patients with COVID-19 who consented to participate. A total of 16 patients (11.42%), had circulating CMV-DNA in peripheral blood at the time of the study. Patients with positive CMV viral load were mainly ICU patients (11/37 -29,7%) and only 5/103 cases (4,85%) were hospitalized into general wards. The accumulated doses of corticosteroids (prednisone equivalents) in the study day were (median and IQR) 987.50 mg (396.87-2,454.68) and 187.50 mg (75.00-818.12) respectively in CMV positive and negative patients ($p < 0.001$). A significant proportion of CMV positive patients were discovered because of the study and were clinically unsuspected by their physicians. The coinfected COVID-CMV positive population had a higher risk of accumulated secondary nosocomially-acquired infections and a worse prognosis.

Conclusion. CMV reactivation should be systematically searched in patients in COVID-19 cases admitted to the ICU.

Keywords: cytomegalovirus, covid-19, nosocomial infection, CMV, CMV reactivation, coinfection.

Correspondence:
Maria Jesus Pérez
Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Doctor Esquerdo, 46
28007 Madrid, Spain
E-mail: massus@hotmail.es

Reactivación de citomegalovirus en pacientes diagnosticados de COVID-19 grave: Un estudio de prevalencia en un hospital general

Objetivo. Determinar la prevalencia de reactivación del CMV en una población ingresada por COVID-19 grave en un hospital general.

Métodos. Estudio de prevalencia en todos los pacientes hospitalizados con COVID-19 (ingresados en salas generales o UCI). Determinación de la presencia de ADN de CMV en sangre. COVID-19 fue confirmado en pacientes con manifestaciones clínicas compatibles, generalmente con neumonía y una prueba de PCR nasofaríngea positiva.

Resultados. Se incluyeron 140 pacientes hospitalizados con COVID-19 que firmaron el consentimiento. Un total de 16 pacientes (11,42%), tenían ADN-CMV circulante en sangre periférica en el momento del estudio. Los pacientes con carga viral CMV positiva eran principalmente pacientes de UCI 11/37 (29,7%) y solo 5/103 casos (4,85%) fueron hospitalizados en salas generaleres. Las dosis acumuladas de corticoides (equivalentes de prednisona), en el día del estudio fueron (mediana y RIQ) 987,50 mg (396,87-2.454,68) y 187,50 mg (75,00-818,12) respectivamente en pacientes con CMV positivo y negativo ($p < 0,001$). Una proporción significativa de pacientes con CMV positivos fueron descubiertos debido al estudio y fueron clínicamente insospechados por sus médicos. La población coinfectada con COVID-CMV positivo tuvo un mayor riesgo de infecciones nosocomiales secundarias acumuladas y un peor pronóstico.

Conclusión. La reactivación de CMV debe buscarse sistemáticamente en pacientes con COVID-19 ingresados en la UCI.

Palabras clave: citomegalovirus, COVID-19, infección nosocomial, CMV, Reactivación de CMV, coinfección.

INTRODUCTION

Symptomatic infection by cytomegalovirus (CMV) occurs mainly as a consequence of the reactivation of latent viruses predominantly as an opportunistic infection in immunosuppressed patients [1-3] . CMV reactivation has also been described in non-primarily immunocompromised patients after long hospital stays mainly in ICUs [4, 5]. In the non-immunosuppressed patients, some studies have demonstrated an association between CMV disease and prolonged mechanical ventilation, increased, associated nosocomial infections, prolonged intensive care unit stay, total length of hospital stay and mortality rates [6].

Surprisingly enough, the information on coinfections of SARS-CoV-2 and CMV or superinfections by CMV in COVID-19 patients have been very scarce. Most reports refer to single cases of Co-infections in ICU patients [7,8], with enteritis or pancreatitis as the main clinical manifestations [9 -11].

In this paper we tried to assess the importance of CMV reactivation in a large population of patients admitted to the hospital due to severe forms of COVID-19.

The aim of the study was to determine the prevalence of CMV reactivation in a population admitted to the hospital for severe COVID 19.

MATERIAL AND METHODS

This is a point prevalence study on the reactivation of CMV infection in patients admitted with severe COVID-19.

Hospital setting and patients. Our institution is a general and referral hospital with 1,350 beds serving a 350.000 inhabitants area of the city of Madrid (Spain). Our center has approximately 50,000 admissions/year.

COVID-19 patients were admitted from March 1st 2020 to the present time in successive waves.

Inclusion criteria to the study. The inclusion criteria were:

- Age ≥18 years
- Admission to hospital (general wards or ICU)
- SARS-CoV-2 infection confirmed by nasopharyngeal PCR test.

In a single day, plasma samples were collected to determine circulating CMV-DNA.

Corticosteroids load was calculated from the time of admission to the study day and converted in equivalent Prednisone dose.

Patients were followed until hospital discharge or death

Laboratory. The method used to determine CMV viral load in blood samples was that of Abbott, "Abbott Real Time PCR CMV" using for extraction the m2000sp and m2000rt for amplification. The lower limit of detection technique is 31 IU / mL (20 copies / mL).

Statistical analysis. Qualitative variables appeared with their frequency distribution. Quantitative variables are expressed as the mean and standard deviation (SD) and as the median and interquartile range (IQR) if their distribution was skewed. Normally distributed continuous variables were compared using the t test; non-normally distributed continuous variables were compared using Mann Whitney test. The chi-squared or Fisher exact test was used to compare categorical variables

Multiple logistic regression analysis was used to assess the risk of positive cytomegalovirus and the variables included were doses of prednisone and hospital stay.

Risk factors for death in a multivariate analysis was determined by including variables that were significant in the univariate analysis.

A ROC curve analysis was employed to evaluate the association of prednisone dose with presence of CMV reactivation.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, New York, USA).

Ethics approval. The local ethics committee of Hospital General Universitario Gregorio Marañón approved the study (MICRO.HGUGM.2020-034). We were provided with a waiver to obtain informed consent.

RESULTS

On the study day, 160 patients with the diagnosis of Covid-19 were admitted in the hospital. Of them, 140 were included in the study (20 were excluded because they were still in the emergency room pending bed assignment) (Table 1).

The majority of our patients were males (64%) with a mean age of 64 years. All patients had been admitted for respiratory failure caused by pneumonia and all were receiving oxygen supplementation by different mechanisms.

Overall, 37 (26%) of the patients were at the ICU on the day of the study. Their underlying conditions are summarized in Table 1. High blood pressure, diabetes mellitus and obesity were the main underlying co-morbidities of the patients. Medium length of hospital stay was 8 days and median ICU stay was 14 days in the study population on the study day.

In the overall population, the accumulated dose of corticosteroids received after hospital admission and up to the study day was 225 mg of prednisone or prednisone equivalents. Tocilizumab was administered to 16 cases (11%).

Of the 140 patients included in the study, 16 (11.42%), patients had a positive CMV viral load in blood on the study day. International units ranged 72 to 3,126 (Min and Max) with a median of 328 (IQR 245.50 to 625.50). Patients with positive CMV viral load were mainly ICU patients (11/37 -29,7%) and only 5/103 cases (4,85%) were hospitalized into general wards.

The situation of CMV reactivation was unknown and clinically unsuspected, before the study day, in 10 out of the 16 positive cases (62.5%). Two cases were already receiving Ganciclovir for evidence of CMV disease.

COVID-19 patients with and without CMV reactivation are compared in Table 1. Significant differences between the CMV positive and CMV negative populations include a longer time of hospital stay at the time of the study in CMV positive cases. The median days of hospital stay in CMV positive and negative reactivation cases were respectively 25.00 (15.00-41.50) versus 7.00 (3.00-14.75); p <0.001. Positive cases were more frequently in the ICU and under mechanical ventilation.

The accumulated doses of corticosteroids (equivalent to prednisone) in the study day were (median and IQR) 987.50 mg (396.87-2,454.68) and 187.50 mg (75.00-818.12) respectively in CMV positive and negative patients (p < 0.001).

Figure 1 correlates the prednisone accumulative dose with the risk of CMV positivity with an AUC of 0.759 (Figure 1).

The CMV positive population had a higher risk of accumulated secondary nosocomially-acquired infections.

Table 1 **Characteristics of patients of the study.**

Patients	Total N= 140	CMV+ N=16	CMV- N= 124	p
Median age in years adults (IQR)	64.00 (53.25-76.00)	63.50 (57.75-74.00)	64.00 (53.00-76.00)	0.587
Sex (%)				
Male	89 (63.57)	11 (68.75)	78 (62.90)	0.786
Female	51 (36.42)	5 (31.25)	46 (37.09)	
ICU (%)	37 (26.42)	11 (68.75)	26 (20.96)	0.001
Patients with MV (%)	27 (19.28)	10 (6.25)	17 (13.70)	<0.001
Days of MV; median (IQR), N=27	21.00 (8.00-32.00)	22.00 (8.50-30.00)	20.00 (7.00-36.50)	0.706
Tocilizumab (%)	16 (11.42)	3 (18.75)	13 (10.48)	0.396
Ganciclovir treatment at the time of the study (%)	8 (5.71)	6 (37.5)	2 (1.61)	<0.001
Dose of prednisone (mg), median (IQR)	225.00 (75.00-918.75)	987.50 (396.87-2,454.68)	187.50 (75.00-818.12)	<0.001
Underlying conditions (%)				
HTA	70 (50.00)	11 (68.75)	59 (47.58)	0.183
Obesity	27 (19.28)	3 (18.75)	24 (19.35)	1.000
Myocardial infarction	3 (2.14)	1 (6.25)	2 (1.61)	0.307
Congestive heart failure	7 (5.00)	0 (0.00)	7 (5.64)	1.000
Central nervous system disease	12 (8.57)	3 (18.75)	9 (7.25)	0.142
Chronic obstructive pulmonary disease	10 (7.14)	1 (6.25)	9 (7.25)	1.000
Renal dysfunction	14 (10.00)	3 (18.75)	11 (8.87)	0.202
Diabetes mellitus	30 (21.42)	6 (37.5)	24 (19.35)	0.111
Peptic ulcer disease	11 (8.85)	0 (0.00)	11 (8.87)	0.364
Peripheral vascular disease	10 (7.14)	0 (0.00)	10 (8.06)	0.604
Tumor	20 (14.28)	4 (25.00)	16 (12.90)	0.247
Median length of hospital stay in days (IQR)	8.00 (4-00-21.00)	25.00 (15.00-41.50)	7.00 (3.00-14.75)	<0.001
Median length of ICU stay in days (IQR)	14.00 (4.75-29.00)	25.00 (9.00-47.00)	11.00 (4.00-23.00)	0.096
Other infections (%)	30 (21.42)	10 (62.5)	20 (16.12)	<0.001
FOLLOW OF PATIENTS				
ICU (%)	44 (31.42)	11 (68.75)	33 (26.6)	0.001
Median length of hospital stay in days (IQR)	15.50 (8.00-39.75)	45.00 (35.25-80.50)	14.00 (7.25-34.00)	<0.001
Median length of ICU stay in days (IQR)	30.00 (11.00-46.00)	39.00 (26.00-78.00)	24.00 (9.00-41.00)	0.029
Other infections (%)	45 (32.14)	12 (75.00)	33 (26.61)	<0.001
Mortality (%)	19 (13.57)	8 (50.0)	11 (8.87)	<0.001

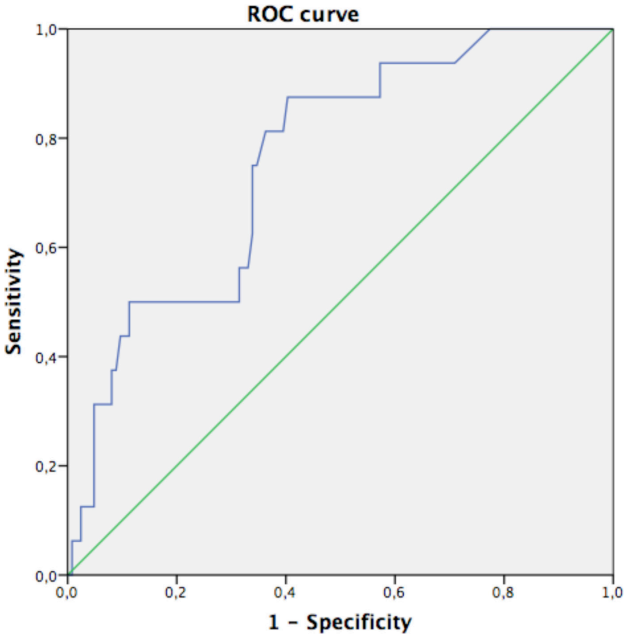

Figure 1 | **Correlates the prednisone accumulative dose with the risk of CMV positivity.**

Table 2 shows the main blood parameters in the COVID-19 patients of the study.

The population evaluated in the study day was followed up until death or discharge from the hospital. Mortality occurred in 19/140 cases (13,57%). In CMV positive cases death occurred in 8/16 cases (50 %) compared with 11/124 (8.87 %) in CMV negative patients (p <0.001).

Comparing the COVID-19 population that died or survived (Table 3), variables independently associated with a poor outcome were: a longer length of stay, higher doses of prednisone and CMV reactivation. In a multivariate analysis, including prednisone dose, hospital stay and CMV, we found that CMV was an independent risk factor for death (Table 4)

DISCUSSION

The results of our study demonstrate that reactivation of CMV is frequent in patients diagnosed with COVID-19, mainly among those that require intensive care. We also show that CMV viremia in COVID-19 patients is frequently clinically unsuspected and under-diagnosed and our study suggest that it is independently associated to a poor clinical outcome.

Primary or reactivated CMV infection is a common problem in the immunocompromised population both in transplant and non-transplant recipients, where preventive and pre-emptive therapy is widely used [12] .

In the populations non-basically immunocompromised, CMV reactivation may occasionally occur in patients with complications and long-term-admissions in ICU [13] . In a study carried out in our own center [5], 16.5% of patients with long ICU stays after major cardiac surgery reactivated CMV and this reactivation was associated with higher mortality, although a causal relationship has not been yet established for this.

Patients with COVID-19 who require hospital admission acquire nosocomial infections in at least 10% of cases and the reactivation of CMV is one of them [14,15] .

The use of corticosteroids is also a well-known cause of CMV reactivation [16,17] and COVID patients requiring long-term admissions frequently receive a liberal use of corticosteroids. They should presumably be excellent candidates for CMV reactivation, but information on this aspect is still scarce [7,11,18,19] .

Table 2 | **Summary of main laboratory results.**

Patients	Total N= 140	CMV+ N= 16	CMV- N= 124	p
Leucocyte count (10E3/µL); median (IQR)	7.28 (5.12-10.52)	10.20 (5.55-13.45)	7.22 (5.10-9.67)	0.092
Lymphocyte count (10E3/µL); median (IQR)	1.00 (0.70-1.50)	1.10 (0.30-1.80)	1.00 (0.70-1.50)	0.868
Lactate; median (IQR)	1.20 (1.00-1.80)	1.20 (0.95-2.17)	1.20 (1.00-1.80)	
C-reactive protein (mg/dL); median (IQR)	3.35 (0.70-8.40)	4.35 (1.07-8.37)	3.15 (0.70-8.62)	0.559
Procalcitonin (µg/L); median (IQR)	0.06 (0.03-0.14)	0.22 (0.07-0.46)	0.05 (0.03-0.12)	0.002
D-dimer (ng/mL); median (IQR)	378.00 (204.00-818.00)	928.00 (307.00-2,597.25)	365.00 (202.00-782.00)	0.019
IL-6 (pg/mL); median (IQR)	17.10 (4.40-51.37)	20.00 (4.20-38.00)	16.60 (4.40-53.70)	0.934
Ferritin (µg/L); median (IQR)	589.00 (280.50-1,024.00)	978.00 (472.00-1,256.00)	547.00 (274.75-942.50)	0.162
Platelets (10E3/µL); median (IQR)	229.00 (152.00-320.00)	158.50 (122.25-229.75)	237.00 (169.00-324.00)	0.018
LDH (u/L); median (IQR)	272.00 (214.75-354.50)	363.00 (270.00-502.50)	269.00 (212.00-330.25)	0.006

IQR, interquartile range.

Table 3 Characteristics of the COVID-19 population that died or survived

Patients	Total N= 140	Exitus N= 19	Vivos N= 121	p
Median age in years adults (IQR)	64.00 (53.25-76.00)	69.00 (64.00-75.00)	62.00 (52.50-76.00)	0.171
Sex (%)				
Male	89 (63.57)	14 (73.68)	75 (61.98)	0.444
Female	51 (36.42)	5 (26.31)	46 (38.01)	
ICU (%)	44 (31.42)	12 (63.15)	32 (26.44)	0.003
Patients with MV (%)	29 (20.71)	11 (57.89)	18 (14.87)	<0.001
Days of MV, median (IQR), N=29	27.00 (23.00-47.00)	34.00 (26.00-53.00)	25.00 (21.50-38.50)	0.264
Tocilizumab (%)	17 (12.14)	5 (26.31)	12 (9.91)	0.057
CMV+ (%)	21 (15.00)	11 (57.89)	10 (8.26)	<0.001
Ganciclovir treatment (%)			5 (4.13)	<0.001
Underlying conditions (%)				
HTA	70 (50.00)	14 (73.68)	56 (46.28)	0.046
Obesity	27 (19.28)	2 (10.52)	25 (20.66)	0.530
Myocardial infarction	3 (2.14)	1 (5.26)	2 (1.65)	0.357
Congestive heart failure	7 (5.00)	1 (5.26)	6 (4.95)	1.000
Central nervous system disease	12 (8.57)	5 (26.31)	7 (5.78)	0.012
Chronic obstructive pulmonary disease	10 (7.14)	1 (5.26)	9 (7.43)	1.000
Renal dysfunction	14 (10.00)	1 (5.26)	13 (10.74)	0.693
Diabetes mellitus	30 (21.42)	4 (21.05)	26 (21.48)	1.000
Peptic ulcer disease	11 (8.85)	1 (5.26)	10 (8.26)	1.000
Peripheral vascular disease	10 (7.14)	2 (10.52)	8 (6.61)	0.626
Tumor	20 (14.28)	5 (26.31)	15 (12.39)	0.151
Median length of hospital stay in days (IQR)	15.50 (8.00-39.75)	42.00 (20.00-66.00)	14.00 (7.50-35.50)	<0.001
Median length of ICU stay in days (IQR)	30.00 (11.00-46.00)	39.00 (30.00-70.00)	24.00 (9.00-39.00)	0.012
Other infections (%)	45 (32.14)	14 (73.68)	31 (25.61)	<0.001

IQR, interquartile range; MV, mechanical ventilation

The existing information on COVID-19 and CMV co-infection is minimal and has been published mainly in the form of isolated clinical cases, in critically ill patients [7,8,20] with variable clinical manifestations. The most common have consisted of the presence of pneumonia [21] , or infection of the gastrointestinal tract with esophagitis, colitis, proctitis, and pancreatitis [9,20,22] ,usually in previously immunocompetent patients.

Cases of SARS-CoV-2 and CMV co-infection have also been reported in patients with pre-existing immunosuppression, such as HIV-infected or transplanted patients who acquired COVID-19 [23,24] or in cases treated with tocilizumab [22].

In a series of 32 cases with COVID-19, the presence of herpes virus viremia, particularly EBV, CMV, and HHV-6, was systematically searched for CMV viremia was detected in 5 patients (15%) shortly after ICU admission and patients with coinfection had more severe forms of the disease and longer intensive care unit stay [25] . In another series of 38 cases in which CMV reactivation was sought, it was demonstrated in two of the cases (5%) [11] .

Some authors speculate on a synergistic mechanism between SARS-CoV-2 and CMV in the development of severe disease [26-28] and in the potential worse prognosis in patients with CMV co-infection [29] .

Our data show that CMV reactivation is frequent in COVID-19 patients requiring intensive care admission but also in patients who do not reach this level of severity and that CMV coinfection is often not suspected clinically since many of the clinical manifestations may be attributable to the COVID-19 itself.

Table 4 **Multivariate logistic regression analysis of death.**

	Odds ratio	β	p-value	IC 95% CI
CMV +	12.31	2.511	<0.001	3.62-41.87
Hospital stay	1.00	0.002	0.875	0.98-1.02
Prednisone dose	0.99	0.000	0.286	0.99-1.00

A limitation of our study is that we enrolled only the population of a single hospital and our data cannot, necessarily, be extrapolated to other populations.

In our opinion, this data suggests that CMV reactivation should be sought systematically in patients with COVID-19 severe enough to require hospital admission, particularly in intensive care and especially in those with a long hospital stay and treated with high dose corticosteroids.

Only prospective studies with therapeutic intervention will be able to demonstrate whether CMV has a causal role in the poor outcome of these patients or whether it is merely an indicator of underlying severity.

We report that a high proportion of patients diagnosed with COVID-19 and admitted to intensive care units have a reactivation of cytomegalovirus. The use of high doses of corticosteroids may have a direct effect on CMV reactivation.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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