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The International Arabic Journal of Antimicrobial Agents
ISSN: 2174-9094

2022
Vol. 12 No. 3:2
doi: 10.3823/868

CMV reactivation in COVID-19 patients: pouring fuel on the fire

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Abstract

Objective: SARS-CoV-2 infection could promote CMV reactivation, worsening disease prognosis. This study aims to identify the potential risk factors of reactivation and mortality outcomes in COVID-19 patients.

Materials and Methods: We included admitted COVID-19 patients in one year period in a tertiary hospital, with clinical criteria of CMV reactivation and positive CMV DNAemia.

Results: Fifteen of 559 COVID-19 patients were diagnosed with CMV reactivation (2.7%). 86.6% were male. Immunodepression was significantly higher in the CMV-positive group (p=0.008). Lymphopenia was significantly higher in CMV positive group (p=<0.001). Ferritin (p=0.019) and IL-6 level (p=0.035) on admission appeared to be significantly lower in this group. ICU admission (p<0.001) and bacterial infections (p<0.001) were significant for CMV reactivation. The mortality was significantly higher in the CMV-positive group (p=0.042).

Conclusion: This study raises the possible incrimination of lymphopenia, immunosuppression, critical illness, and bacterial infections in CMV reactivation.

Received 23-08-2022; Accepted 26-09-2022

Keywords
Cytomegalovirus (Cmv), Reactivation, Covid-19, Lymphopenia, Hyperinflammatory Response.

Introduction

The world has been fighting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic since December 2019, leading to more than 267 million cases and 5 million deaths until now. [1] Its fatality is mainly attributed to the resulting acute respiratory distress syndrome (ARDS), requiring mechanical ventilation and admission to the intensive care unit (ICU). [2] This condition is explained by the severe inflammatory response generated by "the cytokine storm" during a SARS-CoV-2 infection, causing deep tissue damage. [3] All therapeutic efforts were focused to fight against this deleterious inflammatory state, leading to the wide prescription of immunosuppressive molecules, notably corticosteroids, [4] tocilizumab [5], and baricitinib. [6]

Some reports have discussed the involvement of the severe COVID-19 illness along with its treatment modalities, in the reactivation of certain viruses of the Herpesviridae family, such as the cytomegalovirus (CMV), herpes simplex viruses (HSV) [7], and the Epstein-Bar Virus (EBV) in ICU settings. [8]

The identification and the rapid treatment of CMV reactivation are crucial in immunocompromised hosts, especially hematopoietic and organ transplant recipients, as well as in patients living with HIV, given the worse outcome in those groups [9]. Two cases of severe HCMV colitis were reported by Carll et al, [10] and Khatib et al [11] in patients with SARS-CoV-2 infection, highlighting the need to recognize such fatal infections in critical COVID-19 patients. Therefore, this study aims to describe the clinical and biological characteristics of COVID-19 hospitalized patients who developed CMV reactivation in order to identify the responding risk factors and to evaluate the outcome.

Materials and Methods

This monocentric retrospective study was conducted in a tertiary hospital in Beirut, Lebanon, between March 2020 and March 2021.

We included all patients aged above 18 years old, with a confirmed recent SARS-CoV-2 infection by positive RT-PCR on nasopharyngeal or respiratory samples, according to the Infectious Diseases Society of America (IDSA) recommendations for COVID-19 diagnosis [12]. Patients who tested positive for CMV reverse transcription polymerase chain reaction (RT-PCR) on blood samples or on the broncho-alveolar lavage fluid (BALF), performed on the basis of clinical criteria such as respiratory deterioration as defined by an increase in oxygen needs or dyspnea or new infiltrates onset on the chest computed tomography scan (CT scan) associated or not to a fever in a previously stable patient, not responsive to wide spectrum antimicrobial therapy; unexplained persistent gastrointestinal symptoms; or a persistent fever with cytopenia, were diagnosed with a possible CMV reactivation according to the American Society of Transplantation Infectious Diseases Community of Practice guidelines [13] and therefore included in the study. Patients who did not present any clinical symptoms of CMV reactivation during their stay, or who tested negative for CMV RT-PCR are considered to not have a CMV reactivation. The quantification of CMV viral load was done by real-time PCR using the Cobaz z 480 Analyzer with a detection limit of 91 IU/mL.

Subsequently, the patients were divided into two groups whether they were or were not diagnosed with CMV reactivation: COVID/ CMV positive group, and COVID/CMV negative group. We reviewed and collected the data for all included patients using the medical records, after ethical (CEHDF 1846) and administrative agreement. These data included: age and sex, the presence of diabetes or an underlying immunodepression, the inflammatory markers on admission for SARS-CoV-2 infection (IL-6 and ferritin levels and lymphocytes count), the treatments used (corticosteroids, tocilizumab or baricitinib), ICU admission for ARDS, CMV viral load, anti-viral treatments, and duration. The outcome was defined as mortality during admission.

Statistical analysis

The statistical analysis was conducted using IBM SPSS Statistics 26.0. Descriptive statistics were done using Fisher exact test to compare the differences between categorical variables, including: the sex, the presence of diabetes, the presence of an underlying immunodepression, corticosteroids, tocilizumab use, baricitinib use, ICU admission, bacterial infections, and the mortality. The T-test was used to compare the means of the remaining variables. Additionally, logistic regression was used to detect a correlation between the influence of lymphocytes count on admission and the risk of occurrence of CMV reactivation during hospitalization in COVID-19 patients, as well as, to assess the combined risk of corticosteroid treatment dose and duration on CMV reactivation. A two-tailed analysis was used, and Alpha risk was fixed at 5%. In case of missing values, if the percentage of missing values was less than 5%, it was replaced with the mean of the group studied, if it was more than 5% or was a categorical variable the case was removed.

Results

Of the 559 COVID-19 patients admitted during the study period, 15 were diagnosed with a probable CMV reactivation (15/559, 2.7%), according to the American Society of Transplantation Infectious Diseases Community of Practice guidelines, [13] with positive CMV DNAemia, including 3 patients who had simultaneously a positive CMV viral load in broncho-alveolar lavage fluid.

Patient's characteristics

In CMV positive population, thirteen patients (13/15, 86.6%) were male. Six patients were immunocompromised (6/15, 40%), four of which were renal transplant recipients, one had non-Hodgkin lymphoma treated with ongoing chemotherapy and one had myasthenia gravis treated with azathioprine and corticosteroids. Only two patients had a previous history of CMV reactivation, and they were renal transplant recipients. The clinical and biological data of the two groups are presented in **Table 1**.

Table 1. Descriptive and univariate analysis of the clinical and biological data of the two groups.

		COVID/CMV +	COVID/CMV –	p. value
		n=15	n=544	
Mean Age year		63.6	62.8	0.82#
Male Sex	no.	13	362	0.16*
	%	86.6	66.5	
Comorbidities				
Diabetes	no.	6	151	0.38*
	%	40	27	
Immunodeficiency	no.	5	47	0.008*
	%	33	8.6	
COVID-19 inflammatory markers (mean value on admission)				
Lymphocyte count (10*9/L)		0.62	1.17	0.001#
Ferritin level (ng/mL)		818.5	1154.1	0.019#
IL-6 level (pg/mL)		57.08	144.4	0.035#
COVID-19 critical illness				
ICU admission	no.	10	120	<.001*
	%	66	22	
Bacterial infection	no.	11	93	<.001*
	%	73.3	17.1	
COVID-19 specific treatment				
Corticosteroids	no.	14	433	0.32*
	%	93.3	79.5	
Corticosteroids daily dose (dexamethasone equivalent mg)		15.6	14.9	0.91#
Tocilizumab	no.	4	75	0.25*
	%	26.6	13.8	
Baricitinib	no.	2	31	0.22*
	%	13.3	5.7	
mean duration between CMV reactivation and COVID-19 infection-day		33.8 11-74		
Mortality	no.	6	98	0.04*
	%	40	18	
first seven-day follow-up negative CMV-PCR	no.	7	-	-
	%	46.6		

*: Fisher test; #: T test

In a univariate analysis, there was no significant higher percentage for men between the COVID-19 patients who reactivated CMV and those who did not (p=0.16). Also, there was no significant difference in age between the two groups (M=63.6, SD=13.5 for CMV positive vs M=62.8, SD=16.6 for CMV negative, p=0.82).

Risk factors related to the host

The presence of diabetes was not statistically associated with a higher occurrence of CMV reactivation (p=0.38); however, univariate analysis has demonstrated a significantly higher percentage of CMV reactivation in COVID-19 patients with underlying immunodepression (p = 0.008). Although the result is statistically significant, these fields are only weakly associated (effect size 0.137 <0.2 Cramer's V).

Risk factors related to the SARS-CoV-2 illness

Factors related to the inflammatory response

When it comes to inflammatory markers on admission date for SARS-CoV-2 infection, there was a statistically significant higher lymphocyte count in COVID-19/CMV negative group (M=1.16, SD=2522.5), when compared to COVID/CMV positive group (M=0.619, SD=308.7), (p <0.001). The binary logistic regression indicated that a higher lymphocyte count on admission was significantly associated with less risk of reactivation (p=0.019, OR=0.998, 95% CI (0.996-0.999). Therefore, an increase of 0.1× 10^9/L in lymphocyte count on admission decreased the risk of reactivating CMV by 17.18%.

In addition, COVID/CMV positive patients had a statistically significant lower ferritin levels (M= 818.59, SD=412.30) when compared to COVID/CMV negative (M=1154.11, SD=1933.07), p=0.019, and a statistically significant lower IL-6 levels (M= 57.10, SD=39.95) when compared to COVID/CMV negative group (M=144.44, SD=527.62), p=0.035.

Factors related to the SARS-CoV-2 treatments

Corticosteroid's therapy

Fourteen patients (14/15, 93.3%) received corticosteroids, with a mean daily dose equivalent to 15.6 mg of IV dexamethasone (11-37), for a mean duration of 21.9 days (12-37) before the occurrence of CMV reactivation. However, there was no significantly higher percentage of CMV reactivation in COVID-19 patients taking corticosteroids compared to those who did not take them, p= 0.325. There was no significant difference for the corticosteroid's duration, between COVID-19/CMV positive (M=21.9, SD= 7.32) and COVID-19/ CMV negative group (M=21.7, SD= 18.02), p= 0.91. Similarly, no statistical difference was detected for the corticoid daily dose between the two groups (M= 15.6, SD=6.88 for CMV positive vs M=14.9, SD= 9.83 for CMV negative group, p=0.66). Moreover, the binary logistic regression, for corticoid duration (p=0.99, OR=1.00 CI 95% (0.94-1.03)) and the daily dose (p=0.756, OR=1.00 CI 95% (0.96-1.06) did not appear to affect the risk of CMV reactivation in COVID-19 patients receiving corticosteroid treatment.

Corticosteroids with tocilizumab or baricitinib

Four patients (4/15, 26.6%), and 2 patients (2/15, 13.3%), received tocilizumab (p=0.25) and baricitinib (p=0.22) respectively, in addition to corticosteroids with no identified significant difference between the two groups.

Factors related to the critical SARS-CoV-2 illness

Ten patients (10/15, 66.6%) were admitted to the ICU for COVID-19-related ARDS, eight of which (8/15, 53.3%) required mechanical ventilation. A significantly higher percentage of COVID-19 patients admitted to the ICU reactivated CMV (p<0.001, effect size = 0.172 <0.2 weak association Cramer's V).

Eleven patients (11/15, 73.3%) developed a hospital-acquired infection during their hospitalization for COVID-19 infection. This percentage appeared to be

statistically significant for CMV reactivation when compared to the CMV negative group (p<0.001, Effect Size 0.245, moderate association).

CMV reactivation data and related outcome

Thirteen CMV-PCR were performed for respiratory deterioration (13/15), one for persistent unexplained diarrhea, and one for pancytopenia with fever.

CMV reactivation occurred after a mean duration of 33.8 days of the COVID-19 infection. Twelve patients (12/15, 80%) received antiviral therapy, 11 were treated with ganciclovir and one patient with foscarnet due to severe allergic reaction to ganciclovir **(Table 2)**. Two patients had a previous CMV reactivation, both were immunocompromised. Two patients died before CMV-PCR results were obtained; this delay was due to the overworked laboratory during the pandemic period. One patient had a low blood viral load of 216 UI/ml, considered not significant by his treating physician, and therefore didn't require anti-viral therapy. Seven patients had a negative viral load (7/15, 46.6%) on a seven-day PCR follow-up. Two patients had persistent positive viral load requiring an anti-viral treatment for more than 21 days. All CMV reactivation data are presented in **Table 2**. Six patients in the CMV-positive group died during their hospitalization (6/15, 40%).

Table 2. Clinical and microbiologic data of COVID-19 patients diagnosed with CMV reactivation.

Patient	Clinical settings	Immunocompromised	Previous CMV reactivation	Sites	First CMV viral load (UI/mL)	Anti-viral treatment and duration (in days)	Mortality during hospitalization	Comments
1	Respiratory deterioration with sepsis	no	no	blood	261000	Ganciclovir (21 days)	yes	No clinical response
2	Respiratory distress and onset of new pulmonary infiltrates	yes (ongoing chemotherapy for lymphoma)	no	Blood BALF	3970 49300	Ganciclovir (6 days)	yes	no clinical response
3	Respiratory worsening and onset of new pulmonary infiltrates	no	no	Blood BALF	2188 1466000	Ganciclovir (21 days)	no	Negative first follow-up PCR and clinical remission
4	Dyspnea and pulmonary bilateral infiltrates	Yes (renal transplant)	yes	blood	17700	Foscarnet (17 days)	yes	No clinical response
5	Dyspnea and pulmonary bilateral infiltrates	yes (renal transplant)	no	blood	30700	Ganciclovir (21 days)	no	Clinical remission
6	Respiratory deterioration and sepsis	no	no	blood	362000	no	yes	Died before the first PCR result

Patient	Clinical settings	Immunocom-promised	Previous CMV reactivat-ion	Sites	First CMV viral load (UI/mL)	Anti-viral treatment and duration (in days)	Mortality during hospitalization	Comments
7	Persistent unexplained diarrhea	no	no	blood	1800000	Ganciclovir (21 days)	yes	Negative viral load on first follow-up PCR, resolution of the diarrhea.
8	Fever with respiratory deterioration	yes (renal transplant)	no	blood	1800	Ganciclovir (21 days)	no	Negative viral load on first follow-up PCR, clinical remission
9	Respiratory deterioration with new infiltrates	no	no	blood	216	no	no	Viral load (<500 copies/ mL) considered non-significant by the treating physician
10	Respiratory deterioration	no	no	blood	2500	no	yes	Died before the PCR result
11	Fever, dyspnea, new bilateral pulmonary infiltrates	no	no	Blood BALF	2100 6050	Ganciclovir (21 days)	no	Negative viral load on first follow-up PCR
12	Fever, sepsis, bilateral pulmonary infiltrates	yes (renal transplant)	no	blood	16200	Ganciclovir (14 days)	no	Negative viral load on first follow-up PCR
13	Sepsis and respiratory deterioration	no	no	blood	15900	Ganciclovir (60 days)	no	Anti-viral treatment until negative viral load; clinical remission
14	New pulmonary infiltrates	no	no	blood	12300	Ganciclovir (21 days)	no	Negative viral load on first follow-up PCR, clinical remission
15	Fever with pancytopenia	yes (renal transplant)	yes	blood	9500	Ganciclovir (49 days)	no	Anti-viral treatment until negative viral load, clinical improvement

The univariate analysis demonstrated a significant higher mortality percentage of COVID-19 patients in the CMV positive group (p= 0.04, weak association Cramer's V effect size =.093 < 2 weak association). **(Table 1)**

Discussion

The SARS-CoV-2 infection is known to be more severe in men and generally associated with the worst outcomes [14], which could explain the male predominance in the population study. However, CMV reactivation was not significantly more frequent in male COVID-19 patients (p=0.161), nor in a specific age group (p= 0.824).

Many efforts were undertaken to establish appropriate screening and prophylactic treatment guidelines for CMV infections, which occurred mainly in immunocompromised hosts, especially bone marrow and solid organ transplant recipients, increasing the morbidity and mortality rates. [13] Accordingly, this study showed a significantly higher percentage of CMV reactivation in COVID-19 patients who had an underlying immunodepression (p =0.008), which emphasizes the detection of such fatal infection in this vulnerable population after the SARS-CoV-2 infection. However, no other comorbidities, like diabetes, showed a significant association with CMV reactivation in our patients.

When it comes to the SARS-CoV-2 related risk factors, this study showed that lymphopenia was significantly more frequent in the COVID/CMV positive population (p < 0.001). In fact, severe SARS-CoV-2 infection is known to cause lymphopenia, as defined by a lymphocyte count < 1.0×10^9/L. [3] This could explain the increased risk of CMV reactivation in COVID-19 patients, similarly to organ transplant recipients taking immunosuppressive drugs, [15] and patients living with HIV with low T lymphocytes CD4 levels. Although corticosteroid use could further aggravate lymphopenia in such patients, our study did not show any significant difference in the daily dose or the total duration of corticosteroids between the two groups. However, it is noteworthy that the mean daily dose (15.6 mg of dexamethasone), and the mean total duration (21.9 days) used in our center exceeded by far the therapeutic regimen recommended by the IDSA for the management of the severe SARS-CoV-2 infection, which is 6 mg of daily dexamethasone for 10 days. [16] Whilst many reports have suggested the possible benefits of corticoid pulse therapy for hyperinflammation control in critical COVID-19 patients [17–19], randomized trials are still needed to prove its efficacy. Hence, it is important to continuously assess the prescription of such molecules in order to limit the related induced immunosuppression.

Regarding the other immunosuppressive treatments, tocilizumab, a potent IL-6 receptor antibody, was used in our center for the management of the severe SARS-CoV-2 infection nonresponsive to corticosteroids therapy, with an IL-6 level above 30 pg/mL and no evidence of bacterial infection, at a single intravenous dose of 8 mg/kg. There is no currently available data incriminating tocilizumab in the reactivation of CMV infection, as stated by Mourgues et al, who found no significant increase in CMV viral load after treatment with tocilizumab in rheumatoid arthritis patients with longer duration therapy [20]. Also, in our population, there was no significant effect of tocilizumab (p=0.25) nor baricitinib (p=0.22) use regarding CMV reactivation. Besides, the indication of those two treatments could reflect a more serious inflammatory state caused by the SARS-CoV-2 illness, which could by itself increase the risk of CMV reactivation. A recent review article by Forte et al, stated that all hyperinflammatory conditions including oxidative stress, ischemia-reperfusion injury, and bacterial infections could promote CMV reactivation through TNF and NF-κβ stimulation of the major immediate early promoter [9]. A prospective study conducted by Frantzeskaki et al, showed that CMV DNAemia

was present in 13.8% of a group of critically ill, immunocompetent patients [21]. Our study identified a significant higher occurrence of CMV reactivation in ICU admitted patients (p<0.001), and those who developed a bacterial infection during their hospitalization (p< 0.001). Therefore, a review conducted by Mansfield et al has discussed the possible interaction between bacterial infections and CMV reactivation generally occurring 7 to 28 days after the onset of the critical illness, but this hypothesis still needs further studies [22]. In the same perspective, the cytokine storm induced by the SARS-CoV-2 infection could promote CMV reactivation through inflammatory pathway. However, the mean value of ferritin (M= 818.590 vs M=1154.11, p=0.019) and IL-6 levels (M= 57.10 vs M=144.44, p=0.035) were significantly lower in COVID-19 patients reactivating CMV. In fact, we only mentioned the values on admission which could become higher later during the progression of the inflammatory process, and affect the statistical analysis, in addition to the small sample effect.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interest

The authors declare no competing interest.

Availability of data and material:

N/A

Ethics approval

Approval was obtained from the local ethics committee (CEHDF 1846)

Authors' contributions

R.I, M.C and E.H conceived of the presented idea; E.L performed the statistical analysis; R.I. wrote the manuscript with support from MA.G and E.L; Z.BC, C.H and R.K collected the data; E.H, G.S and J.C supervised the project and contributed to the final version of the manuscript.

Consent to participate

N/A

Consent for publication

All authors give their approval for the publication of the article data in this journal.

Acknowledgment

The authors would like to acknowledge the infectious diseases, pulmonary and critical care departments at Hotel-Dieu de France hospital for providing the data about the COVID-19 patients.

References

1. WHO Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int accessed December 10, 2021.
2. Batah SS, Fabro AT. Pulmonary pathology of ARDS in COVID-19: A pathological review for clinicians. Respir Med. 2021 Jan ;176 :106239. doi: 10.1016/j.rmed.2020.106239
3. Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020 Jun; 11: 01446 doi:10.3389/fimmu.2020.01446
4. P, Horby, Lim Ws, Emberson Jr, et al. et al. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2021 Nov 27;384(8); doi:10.1056/NEJMoa2021436
5. C, Zhang, Wu Z, Li Jw, Zhao H, and Wang Gq. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2021 Nov 27;55(5); doi: 10.1016/j.ijantimicag.2020.105954.
6. Cantini F, Niccoli L, Nannini C, et al. Beneficial impact of Baricitinib in COVID-19 moderate pneumonia; multicentre study. J Infect. 2020;81(4):647-679. doi:10.1016/j.jinf.2020.06.052
7. Le Balc'h P, Pinceaux K, Pronier C, Seguin P, Tadié J-M, Reizine F. Herpes simplex virus and cytomegalovirus reactivations among severe COVID-19 patients. Crit Care. 2020 Aug 28;24(1):530.
8. Jh, Naendrup, Borrega Jorge G, Dennis Alexander E, et al. Reactivation of EBV and CMV in Severe COVID-19-Epiphenomena or Trigger of Hyperinflammation in Need of Treatment? A Large Case Series of Critically ill Patients. J Intensive Care Med. 2021 Nov 18; doi:10.1177/08850666211053990

9. E, Forte, Zhang Z, Thorp Eb, and Hummel M. Cytomegalovirus Latency and Reactivation: An Intricate Interplay With the Host Immune Response. Front Cell Infect Microbiol [Internet]. 2020 Mar 31;10; doi:10.3389/fcimb.2020.00130
10. Wc, Carll, Rady My, Salomao Ma, et al.. Cytomegalovirus haemorrhagic enterocolitis associated with severe infection with COVID-19. BMJ Open Gastroenterol. 2021 Jan;8(1); doi:10.1136/bmjgast-2020-000556
11. My, Khatib, Shaik Ks, Ahmed Aa, et al, et al. Tocilizumab-induced cytomegalovirus colitis in a patient with COVID-19. Clin Case Rep 2020;9(1); doi:10.1002/ccr3.3487
12. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19 [Internet]. [cited 2021 Nov 27]. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-diagnostics/
13. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019;33(9); doi:10.1111/ctr.13512
14. Foresta C, Rocca MS, Di Nisio A. Gender susceptibility to COVID-19: a review of the putative role of sex hormones and X chromosome. J Endocrinol Invest. 2021 May 1;44(5):951–6.
15. Iwatani Y, Amemiya N, Nokiba H, Yamazaki M, Sugiura H, Nitta K. Risk factors for cytomegalovirus reactivation in patients with kidney disease under immunosuppressive therapy. Clin Exp Nephrol 2021 Aug 3; doi:10.1007/s10157-021-02117-5
16. COVID-19 Guideline, Part 1: Treatment and Management. Available from: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ accessed November 27, 2021
17. O, Gundogdu, Demir B, Coskun Co, and Ersan I. Efficacy of pulse steroid therapy in patients critically ill with COVID-19. Bratisl Lek Listy 2021;122(11); doi:10.4149/BLL_2021_126
18. Má, López Zúñiga, Moreno-Moral A, Ocaña-Granados A, et al. High-dose corticosteroid pulse therapy increases the survival rate in COVID-19 patients at risk of hyper-inflammatory response. PloS One 2021;16(1). doi:10.1371/journal.pone.0243964
19. Vy, Mareev, Orlova Ya, Pavlikova Ep, et al. Steroid pulse -therapy in patients With coronAvirus Pneumonia (COVID-19), sYstemic inFlammation And Risk of vEnous thRombosis and thromboembolism (WAYFARER Study). Kardiologiia 2020 Jul 7;60(6). doi:10.18087/cardio.2020.6.n1226
20. Scherlinger M, Alain S, and Richez C Monitoring of Epstein-Barr virus (EBV)/cytomegalovirus (CMV)/varicella-zoster virus (VZV) load in patients receiving tocilizumab for rheumatoid arthritis Joint Bone Spine 2018 Mar;85(2):259-260; doi: 10.1016/j.jbspin.2017.02.010. Epub 2017 Mar 28.
21. Fg, Frantzeskaki, Karampi Es, Kottaridi C, et al. Cytomegalovirus reactivation in a general, non-immunosuppressed intensive care unit population: incidence, risk factors, associations with organ dysfunction, and inflammatory biomarkers. J Crit Care. 2015 Apr;30(2). doi:10.1016/j.jcrc.2014.10.002
22. Mansfield S, Grießl M, Gutknecht M, Cook CH. Sepsis and cytomegalovirus: foes or conspirators? Med Microbiol Immunol (Berl). 2015 Jun;204(3):431–7.