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Research Article / Araştırma

The Importance of CMV Reactivation in COVID-19-Related ARDS Patients

COVID-19 İlişkili Akut Solunum Sıkıntısı Sendromu Hastalarında Sitomegalovirüs Reaktivasyonunun Önemi

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ABSTRACT

Objectives: Cytomegalovirus (CMV) reactivation is a significant cause of morbidity and mortality in critically ill patients. Existing or newly developed immunosuppression appears to be the main factor for reactivation. COVID-19 patients with acute respiratory distress syndrome can be affected by a variety of conditions that cause immunosuppression. Clarifying CMV reactivation and notably its predictive features became important during the epidemic.

Methods: This is a retrospective, observational, and cohort study. All COVID-19 patients admitted to the ICU between March 11, 2020 and March 11, 2021 were analyzed. All of the information was gathered from the hospital's electronic records. CMV reactivation was defined as CMV DNA ≥1000 copies/ml in tracheal samples. The patient population was analyzed in two groups, namely, patients with CMV reactivation and patients without reactivation.

Results: During the study period, 99 of all COVID-19 ARDS patients fulfilled the inclusion criteria, and CMV reactivation was detected in 55 (55.6%) of them. Age, BMI, APACHE-II score, hypertension, chronic respiratory disease, the usage of interleukin blockers, the duration of steroid usage, procalcitonin (PCT), and CD-8 T-cell levels differed significantly from the patients without CMV reactivation. Furthermore, the reactivation group had longer ICU stays, longer durations of mechanical ventilation, and higher mortality.

Conclusion: CMV can be reactivated in critically ill COVID-19 ARDS patients, which appears to correlate with worse outcomes. Obesity, the usage of IL-blockers and steroids >12 days, high PCT, and low CD-8 T-cell levels appear to be risk factors. Critically ill COVID-19 patients should be closely monitored with regard to immunosuppression and CMV status.

Keywords: COVID-19, cytomegalovirus, immunosuppression, latent infection

ÖZ

Amaç: Sitomegalovirüs reaktivasyonu, kritik hastalarda önemli bir morbidite ve mortalite nedeni olarak karşımıza çıkmaktadır. Reaktivasyon için en önemli faktörlerden biri yeni gelişmiş veya var olan immünsüpresyondur. Akut solunum sıkıntısı sendromu olan koronavirüs hastalığı-19 (COVID-19) hastaları, immünsüpresyona neden olan çeşitli koşullardan etkilenebilir. Sitomegalovirüs reaktivasyonunun ve özellikle tahmin edici özelliklerinin netleştirilmesi, özellikle pandemi döneminde önem kazandı.

Yöntem: Bu çalışma, retrospektif ve gözlemsel bir kohort çalışmasıdır. 11 Mart 2020 ile 11 Mart 2021 tarihleri arasında yoğun bakım ünitesine kabul edilen COVID-19 hastaları değerlendirildi. Tüm hasta bilgileri hastanenin elektronik kayıtlarından elde edildi. Trakeal örneklerde CMV DNA'nın ≥ 1000 kopya/mL olarak saptanması sitomegalovirüs reaktivasyonu olarak tanımlandı. Hastalar sitomegalovirüs reaktivasyonu olan ve olmayan hastalar olarak iki grupta değerlendirildi.

Bulgular: Çalışma süresi boyunca, tüm COVID-19 akut solunum sıkıntısı sendromu hastalarından sadece 99'u çalışmaya dahil edilme kriterlerini karşıladı ve 55 hastada (%55,6) sitomegalovirüs reaktivasyonu tespit edildi. Sitomegalovirüs reaktivasyonu saptanan hastalarda, yaş, beden kitle indeksi, APACHE-II skoru, hipertansiyon, kronik solunum yolu hastalığı, interlökin bloker kullanımı, steroid kullanım süresi, prokalsitonin ve T hücre düzeyi (CD-8) sitomegalovirüs reaktivasyonu olmayan hastalardan önemli ölçüde farklıydı. Ayrıca, sitomegalovirüs reaktivasyon grubundaki hastaların daha uzun yoğun bakım ve mekanik ventilasyon süresi ve daha yüksek mortaliteye sahip oldukları gözlemlendi.

Sonuç: COVID-19 ilişkili akut solunum sıkıntısı sendromu hastalarında sitomegalovirüs reaktivasyonu görülebilir ve bu durumun daha kötü sonuçlarla ilişkili olduğu tespit edilmiştir. İnterlökin veya 12 günden fazla steroid kullanımı, obezite, yüksek prokalsitonin ve düşük CD-8 T lenfosit düzeyleri reaktivasyon için risk faktörleridir. Yoğun bakımda COVID-19 hastaları immünsüpresyon ve sitomegalovirüs reaktivasyonu açısından yakın izlenmelidir.

Anahtar sözcükler: COVID-19, immünsüpresyon, latent infeksiyon, sitomegalovirüs

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Introduction

Cytomegalovirus (CMV) reactivation is a significant cause of morbidity and mortality in critically ill patients.[1] Its main cause appears to be immunosuppression: CMV reactivation is more common in cases of immunosuppression and loss of T-cell immune surveillance,[2] but its presence before intensive care unit (ICU) admission is not necessary for CMV reactivation.[3] Critically ill patients can exhibit signals such as apoptosis, hypoxia, or metabolic stress, which can trigger cellular response,[2] suppressing immunity. Frantzeska et al.[3] investigated the relationship between immunity and the degree of stress and CMV reactivation. Apart from stress, in the ICU, many risk factors can be considered, such as sepsis,[4,5] septic shock,[6] or the use of drugs that can suppress immunity.[7] In critically ill COVID-19 patients, in addition to these factors, the natural course of SARS-CoV-2 infection can also lead to immunosuppression.[8] Because we also know that CMV reactivation worsens outcomes,[9] knowing these risk factors will enable us to more closely follow at-risk patients. During the pandemic, when there were problems from time to time in finding intensive care beds, clarifying CMV reactivation became beneficial. Further, it remains to be determined whether CMV reactivation causes mortality or merely accompanies a high mortality rate.

Thus, we aimed to investigate the prevalence and outcomes of CMV reactivation in critically ill COVID-19 patients and to detect the predictors of the same.

Methods

This is a retrospective, observational, and cohort study, approved by The Ministry of Health, and the Ethics Committee found it to be ethically appropriate on December 17, 2020 (decision number 2020-26/33). The retrospective nature of the study could not prevent receiving written patient consent.

All COVID-19 patients admitted to the ICU between March 11, 2020 and March 11, 2021 were analyzed. We include in the study only >18 years old intubated COVID-19 patients, with acute respiratory distress syndrome (with Horowitz index <200), after 2 weeks' stay in the ICU still with bilateral pulmonary infiltrates in all lung quadrants and with bone marrow suppression that other causes cannot explain. Patients with known immunosuppression, such as cancer patients or those chronically receiving immunosuppressive agents, were excluded from the study.

We recorded demographic data, ICU admission scores, comorbidities, laboratory parameters, and the usage of interleukin (IL) blockers and steroids from the hospital's electronic data. Intensive care duration, outcomes, and mortality of all patients were also recorded. In our routine practice, CMV reactivation has been assessed by detection of viral DNA using real-time polymerase chain reaction (PCR) in deep tracheal aspirate samples. We follow the patients with positive CMV DNA for an increase of DNA log values if detected >0.5 log, then we evaluate these parameters with the clinical condition of the patient and start antiviral treatment. In our study, CMV reactivation was defined as CMV DNA ≥1000 copies/ml in bronchoalveolar lavage samples.

The patient population was analyzed in two groups, namely, patients with CMV reactivation and patients without reactivation. We performed statistical analyses using SPSS, Version 23.0 (IBM Corp., Armonk, NY, USA). Data are presented as means, medians, and interquartile ranges according to the distribution of the values. Kolmogorov-Smirnov test was used for the detection of normal distribution. For both groups' analyses, we used student t, Chi-square, and Mann-Whitney U tests. For CMV-reactivation, cutoff and area under curve values of all significant variables in the CMV-reactivation group were detected using ROC curve analysis. We added all significantly different parameters in the CMV-reactivation group into a multivariate logistic regression model of the likelihood of CMV reactivation. Consideration for statistical significance was p=0.05.

Results

During the study period, 250 COVID-19 patients were admitted to our ICU, and 99 of them were eligible for the study (Fig. 1). CMV reactivation was detected in 55 (55.6%) of these 99 patients. That is, CMV DNA was detected in 55 patients, which amounts to 55.6% of suspected patients, and 22% of all ICU admitted patients. All the demographic and clinical details are presented in Table 1.

When the demographic data were evaluated, there was a significant difference in terms of age (p=0.002). Further-

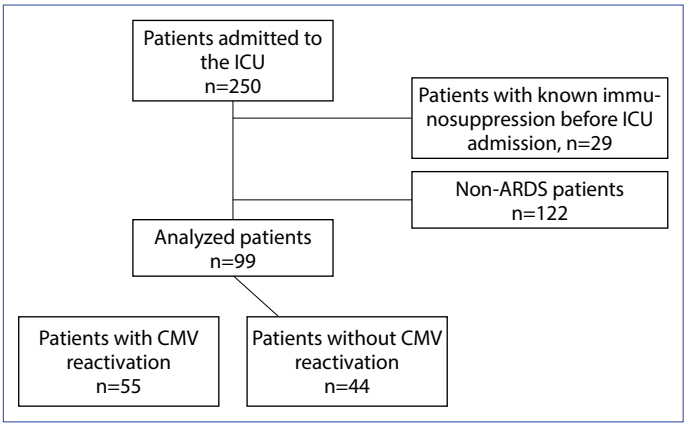

Figure 1. Study flowchart.
ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; CMV: Cytomegalovirus.

Table 1. Characteristics of patients groups

Characteristics	Patients without CMV reactivation (n=44)		Patients with CMV reactivation (n=55)		p
	n	%	n	%	
Age, years	65	52-74	70	66-78	0.002
Male	32	72.7	50	90.9	0.060
BMI (kg/m^2)	25.9	24.8-27.5	27.6	26.2-29.1	0.001
APACHE II	19	16-22	23	17-27	0.030
SOFA score	7	6-9	7	6-8	0.635
Comorbidities					
Hypertension	22	50.0	40	72.7	0.020
Diabetes mellitus	16	36.4	28	50.9	0.148
Cancer	2	4.5	8	14.5	0.178
Ischemic heart disease	8	18.2	20	36.4	0.046
Chronic respiratory disease	4	9.1	14	25.5	0.040
Laboratory findings					
WBC	10.4	7.2-14.4	11.4	8.7-14.3	0.449
Lymphocyte count	0.72	0.47-1.00	0.70	0.49-0.91	0.871
C-reactive protein, (mg/dL)	13.6±9.4		13.3±10.3		0.866
Procalcitonin, (ng/mL)	0.13	0.04-0.36	0.24	0.09-0.70	0.030
Ferritin, (ng/mL)	943	351-1553	973	514-1614	0.477
D-dimer, (mg/L)	1.4	0.7-2.2	1.9	1.0-4.2	0.074
Lactate dehydrogenase, (U/L)	398	302-573	429	317-547	0.684
IL-6	55	15-155	69	25-280	0.224
CD4-T-cell	269	159-368	208	132-400	0.206
CD8-T-cell	150	92-194	79	48-148	<0.001
Additional therapies					
IL-blockers	3	6.8	19	34.5	0.001
Dexamethasone	12	27.3	20	36.4	0.337
Methylprednisolone	38	86.4	48	87.3	0.894
Dexamethasone plus methylprednisolone (days)	10	8-15	14	8-24	0.020
Pulse steroid	5	11.4	14	25.5	0.077
Therapeutic plasma exchange	7	15.9	14	25.5	0.248
Outcomes					
The usage of vasopressor	40	90.9	55	100.0	0.022
Continuous renal replacement therapy	11	25.0	30	54.5	0.003
Duration of MV, days	10	7-18	23	15-32	0.001
Length of ICU, days	13	9-21	23	19-32	0.001
Mortality	14	31.8	38	69.1	0.001

Values are presented as Mean±SD, median (quartiles) or n, %. CMV: Cytomegalovirus; BMI: Body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA Score: Sequential Organ Failure Assessment Score; WBC: White blood cells; IL-6: Interleukin 6; MV: Mechanical ventilation; ICU: Intensive care unit.

more, CMV-reactivated patients had higher body mass indices (BMIs) (p=0.001) and Acute Physiology And Chronic Health Evaluation II (APACHE II) values (p=0.030). No difference was found in the Sequential Organ Failure Assessment score (p=0.635). Comorbidities, such as hypertension (p=0.020), ischemic heart disease (p=0.046), and chronic respiratory disease (p=0.040), were found to be more common in the CMV-reactivation group (Table 1).

There were no significant differences between COVID-19 patients with and without CMV reactivation with respect to inflammatory parameters, except procalcitonin (PCT), which was significantly higher in the reactivation group (p=0.030). Furthermore, patients with CMV reactivation had lower levels of CD-8 T cells (p<0.001). Some additional therapies, such as the use of IL-blockers (p=0.020) and steroids (p=0.020), were found to be significantly different.

One interesting result regarding steroid usage is that, even when pulse steroid therapy had not made a difference, the separate use of dexamethasone and methylprednisolone was found to correlate with reactivation (p=0.020).

When looking at the outcomes, patients with CMV reactivation had longer stays in the ICU (p<0.001), longer duration of mechanical ventilation (p<0.001), and higher mortality than patients without CMV reactivation (p<0.001). Mortality in CMV-positive patients was found to be 38 (69.0); in all suspected patients, this value was 52 (52.5). Furthermore, in these patients, the usage of vasopressor (p<0.022) and continuous renal replacement therapy (p<0.022) was statistically significant.

To detection of CMV reactivation, the cutoff and the areas under the curve values for age, BMI, CD8 T-cell level, the usage of steroid, the usage of IL-blocker, APACHE II, and PCT were > 68 (0.68 [0.57-0.80]); ≥26.7 (0.69 [0.59-0.80]); ≤115 0.70 [0.59-0.80]); ≥ 12 days (0.64 [0.53-0.75]). The usage of IL-blocker (0.64 [0.53-0.75]); ≥21 (0.63 [0.52-0.74]); and ≥0.18 (0.63 [0.52-0.74]), respectively, (p=0.002, p=0.001, p=0.001, p=0.020, p=0.020, p=0.030, and p=0.030, respectively) (Table 2).

The risk ratio for mortality due to CMV reactivation was found as 2.4 (1.4-3.9) (p=0.001).

In the multivariate logistic regression model, the likelihood of CMV reactivation was 8.0-fold, 4.6-fold, 4.3-fold, 4.0-fold, and 3.6-fold increased by the usage of IL-blockers, BMI ≥26.7, PCT ≥0.18, steroid usage ≥12 days, and CD-8 T-cell level ≤115 (p=0.037, p=0.01, p=0.026, p=0.042, and p=0.024), respectively (Table 3).

Table 2. The cut-off and AUC values of variables for the detection of CMV reactivation

Parameters	AUC (CI 95%)	p
Age>68	0.68 (0.57-0.80)	0.002
BMI≥26.7	0.69 (0.59-0.80)	0.001
CD8 T-cell≤115	0.70 (0.59-0.80)	0.001
The usage of steroid ≥12 days	0.64 (0.53-0.75)	0.020
The usage of IL-blocker	0.64 (0.53-0.75)	0.020
APACHE II≥21	0.63 (0.52-0.74)	0.030
Procalcitonin≥0.18	0.63 (0.52-0.74)	0.030

AUC: Area under curve; CI: Confidence interval; CMV: Cytomegalovirus; BMI: Body mass index; CD8: Cluster of differentiation 8; APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 3. Multivariate logistic regression model for likelihood of CMV reactivation

Variable	OR (CI 95%)	p
The usage of IL-blocker	8.0 (1.1-56.4)	0.037
BMI ≥26.7	4.6 (1.4-14.6)	0.010
Procalcitonin ≥0.18	4.3 (1.2-15.8)	0.026
The usage of steroid ≥12 days	4.0 (1.1-14.9)	0.042
CD-8 T-cell≤115	3.6 (1.2-10.9)	0.024

CMV: Cytomegalovirus; CI: Confidence interval; OR: Odds ratio; BMI: Body mass index; CD-8: Cluster of differentiation 8.

Discussion

This is the first larger study to investigate the prevalence and outcomes of CMV reactivation in critically ill COVID-19 ARDS patients and to detect the predictors of the same. Our results show that assessing some parameters in COVID-19 ARDS patients could be valuable in the early diagnosis and outcome prediction of CMV reactivation. Debates about the pathogenicity of CMV reactivation continue, but it is well known that these patients have prolonged mechanical ventilation[1,9] and higher mortality.[10,11] Frantzeskaki et al.[3] show that CMV reactivation can be seen in critically ill patients without pre-existing immunosuppression. Whether newly developed or previously known, the most apparent cause of reactivation appears to be immunosuppression. Indeed, patients with immunosuppressive diseases are more susceptible to CMV reactivation when risk factors are added.[12] The seroprevalence of CMV infection is 56.7%;[13] therefore, the majority of the patients with long-term ICU durations are at risk for this mortal reactivation. Considering that thousands of immunocompetent people suffer a critical illness every day due to severe COVID-19 and that CMV's prevalence and associated factors are known, this is valuable information. It is difficult to predict the extent of immunosuppression and in which patients' CMV will occur. Still, it would be beneficial to determine the related risk factors and more closely monitor at-risk patients.

The immunity-lowering effect of SARS-CoV-2 has been demonstrated in some studies[8,14] and continues to be investigated. Interaction between the virus and host cells determines the immune response essential in recovery.[15] Cell-mediated immunity is inadequate in the elderly and can explain their susceptibility to more severe infections.[16] Sometimes, exaggerating this response can also cause harm,[15] which explains COVID-19 patients' immune response dysregulation and hyper inflammation.[17] The uncontrolled inflammatory response is accompanied by decreased CD-4 and CD-8 T-cell levels and immune activation.[18] In our study, we noticed severely low CD-4 and CD-8 in some of the patients we followed up with, and we found that the CD-8 level was related to reactivation. Diao et al.[19] also report that numerical reduction and functional impairment in T-cells can affect a state of acquired immune deficiency, leading to superinfections and reactivations. Cytokines have been implicated in Herpesviridae family reactivation;[20] on the other hand, CMV can also produce in-

flammatory mediators,[21] sustaining infection and further inhibiting host immunity. With these mechanisms triggering one another, the patient seems to be in a blind loop.

Experiencing the effects of anti-inflammatories and IL-blockers, which are used to suppress hyperinflammation, may also develop immunosuppression, which may indirectly trigger the reactivation. Agents used to suppress hyperinflammation in our group of COVID-19 patients were tocilizumab and steroids. We found that the usage of steroids significantly correlates with CMV reactivation (p=0.020). Steroids cause macrophage and T-lymphocyte apoptosis to impair T-lymphocyte function and inhibit the production of many inflammatory cytokines.[22] Tocilizumab was reported not to increase CMV reactivation:[23] We found a higher usage of IL-blockers in the reactivation group (p=0.020). However, this funding can be explained by the fact that patients who receive tocilizumab have more severe diseases.

Mortality prediction in ICU patients is difficult, but intensive care severity scores - especially APACHE scores-can serve as a guide.[24] Unlike in previous studies,[25] we found that APACHE II scores were significantly different in the CMV-reactivation group. In our opinion, this result is attributable to the homogeneity of the patient population included in the study; therefore, the number and extent of organ dysfunctions are similar. The significant differences in BMI were not surprising, because, during the H1N1 pandemic, BMI was one of the most important factors for increased morbidity and mortality.[26]

CMV was observed in 22% of all ICU patients in this study, which result is lower than that reported by Kalil and Florescu in their study, who showed that one in three latently infected critically ill patients would experience CMV reactivation during their critical illness.[27] In line with the previous reports, we found that CMV reactivation correlates with worsened outcomes and increased mortality (p<0.001). The lungs are a primary site of latent viral presence and a commonplace of reactivation, which can explain the association between CMV reactivation and an increased duration of mechanical ventilation and ARDS.[28] Therefore, at-risk patients should be more closely followed up with using PCR controls to check for CMV reactivation. To prove it, CMV DNA positivity should be used to evaluate the patients' clinical condition. Our study has strengths that deserve highlighting: first, this is, the first larger study to assess potential associations between CMV reactivation and COVID-19 patients; second, the studied patient population is homogeneous, having the same admission diagnoses.

The main limitations of our study are its retrospective nature and the lack of samples from other places that could isolate the virus such as urine, saliva, stool, or plasma samples. However, despite these limitations, this study may help increase awareness of possible viral reactivations in critically ill patients.

Conclusion

IL-blockers, prolonged steroid usage, obesity, high PCT, and low CD-8 T-cell levels appear as risk factors for CMV reactivation in critically ill COVID-19 patients, who seem to be correlated with worse outcomes. Despite this evidence, we cannot say whether CMV is a pathogen in these patients or just a bystander. In any case, these patients should be closely monitored with regard to immunosuppression and CMV status. Further prospective studies must broadly define CMV-related risks in critically ill COVID-19 patients and develop therapeutic strategies.

Disclosures

Ethics Committee Approval: The study was approved by The Acıbadem Mehmet Ali Aydinlar University Ethics Committee (Date: 17/12/2020, No: 2020-26/33).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Authorship Contributions: Concept – L.D., Z.T.S.; Design – L.D., B.G.; Supervision – L.D., İ.Ö.A.; Fundings – L.D., Z.T.S.; Materials – L.D., Z.T.S.; Data collection &/or processing – L.D., Z.T.S.; Analysis and/or interpretation – B.G., İ.Ö.A.; Literature search – L.D., B.G.; Writing – L.D., İ.Ö.A.; Critical review – B.G., İ.Ö.A.

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