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ANALYSIS OF CLINICAL AND EPIDEMIOLOGICAL FEATURES OF HERPESVIRUS REACTIVATION IN INDIVIDUALS WITH A HISTORY OF COVID-19

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Abstract

Introduction. Herpesvirus reactivation in patients with a history of Coronavirus disease (COVID-19) is an increasingly recognized problem that may exacerbate the clinical manifestations of post-COVID syndrome. Reactivation of latent viruses such as herpes simplex virus (HSV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV) has been frequently observed, but the clinical and epidemiological features of this phenomenon remain insufficiently studied.

Objective. To investigate the clinical and epidemiological characteristics of herpesvirus reactivation (CMV, EBV, HSV) in patients after COVID-19, based on a comprehensive analysis of symptoms and laboratory findings.

Methods. A retrospective analytical case–control study was conducted, including 80 patients, of whom 40 comprised the main group with a confirmed history of COVID-19, and 40 formed the control group without any indication of previous COVID-19. The analysis included the assessment of clinical symptoms, results of specific immunological testing by enzyme-linked immunosorbent assay (ELISA) for IgG and IgM antibodies to herpesviruses, as well as laboratory parameters, including complete blood count and biochemical profile. Statistical analysis was performed using nonparametric tests, including the Mann–Whitney U test and Pearson's chi-square test. Statistical significance was set at $p < 0.05$.

Results. Cytomegalovirus was the most frequently reactivated herpesvirus (30%). Reactivation occurred significantly more often in patients with moderate to severe COVID-19 compared to those with mild disease (*75% vs. 33.3%; $p = 0.036$*). Patients with reactivation more frequently presented with peripheral lymphadenopathy (*85% vs. 47.5%; $p = 0.0009$*) and febrile fever (*25% vs. 5%; $p = 0.028$*). Serological testing revealed elevated IgG titers with high optical density and absence of IgM, indicating reactivation. CRP (*$p = 0.002$*) and blood glucose (*$p = 0.035$*) levels were also significantly higher in the reactivation group.

Conclusion. The study identified a range of clinical and laboratory features associated with herpesvirus reactivation in patients following COVID-19. These findings highlight the relevance of comprehensive post-COVID assessment, considering potential interactions between SARS-CoV-2 and latent viruses, and support the inclusion of herpesvirus screening in post-COVID monitoring protocols.

Keywords: *post-COVID syndrome; herpesvirus infections; risk factors; COVID-19; viral reactivation*

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Резюме

АНАЛИЗ КЛИНИКО-ЭПИДЕМИОЛОГИЧЕСКИХ ПРИЗНАКОВ РЕАКТИВАЦИИ ГЕРПЕСВИРУСОВ У ЛИЦ, ПЕРЕНЁСШИХ COVID-19

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Введение: Реактивация герпесвирусных инфекций у пациентов, перенёсших COVID-19, рассматривается как одно из потенциальных осложнений постковидного периода, способное усиливать системную воспалительную реакцию и пролонгировать клинические проявления. Наиболее часто в этом контексте обсуждаются вирус простого герпеса (ВПГ), вирус Эпштейна–Барр (ВЭБ) и цитомегаловирус (ЦМВ), способные к реактивации на фоне иммунной дисрегуляции, индуцированной SARS-CoV-2.

Цель исследования: Изучить клинико-эпидемиологические особенности реактивации герпесвирусных инфекций (ЦМВ,ВПГ,ВЭБ) у пациентов после перенесённой коронавирусной инфекции на основе комплексного анализа симптоматики, лабораторных данных.

Методы: Проведено ретроспективное аналитическое исследование по типу «случай–контроль» с включением 80 пациентов, из которых 40 составили основную группу с подтверждённой в анамнезе COVID-19, а 40- контрольную группу без указаний на перенесённый COVID-19. Статистическая обработка данных проводилась с применением непараметрических методов, включая критерий Манна–Уитни и χ^2 Пирсона; уровень значимости считался статистически достоверным при $p < 0,05$.

Результаты: В ходе анализа установлено, что реактивация герпесвирусных инфекций достоверно чаще наблюдалась у пациентов, перенёсших COVID-19 средней и тяжёлой степени тяжести, по сравнению с пациентами, перенёсшими лёгкую форму заболевания (75% против 33,3%). В клинической картине таких пациентов значительно чаще регистрировались признаки периферической лимфоаденопатии (85% против 47,5%) и фебрильной лихорадки (25% против 5%). По данным серологического обследования выявлено преобладание высоких уровней IgG с увеличенной оптической плотностью и сниженной авидностью, что соответствует признакам реактивации латентной герпесвирусной инфекции.

Выводы: Проведённое исследование позволило выделить ряд клинико-эпидемиологических и лабораторных особенностей, ассоциированных с реактивацией герпесвирусных инфекций у пациентов после перенесённого COVID-19. Установлена актуальность комплексной оценки состояния пациентов в постковидном периоде с учётом возможного взаимодействия SARS-CoV-2 с латентными вирусами. Полученные данные могут служить основанием для дальнейших исследований в данном направлении и целесообразности внедрения скрининга на герпесвирусные инфекции в практику постковидного мониторинга.

Ключевые слова: *постковидный синдром; герпесвирусные инфекции; факторы риска, COVID-19, реактивация вирусов.*

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Түйіндеме

COVID-19-ДАН КЕЙІНГІ ГЕРПЕСВИРУС ИНФЕКЦИЯЛАРЫНЫҢ РЕАКТИВАЦИЯСЫНЫҢ КЛИНИКО-ЭПИДЕМИОЛОГИЯЛЫҚ БЕЛГІЛЕРІН ТАЛДАУ

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Кіріспе: COVID-19-бен ауырған науқастарда герпесвирус инфекцияларының реактивациясы постковид кезеңінің ықтимал асқынуларының бірі ретінде қарастырылады. Бұл жағдай жүйелік қабыну реакциясын күшейтіп, клиникалық белгілердің ұзақ сақталуына әкелуі мүмкін. Бұл контексте жиі қозғалатын вирус түрлеріне жай герпес вирусы (ЖГВ), Эпштейн–Барр вирусы (ЭББ) және цитомегаловирус (ЦМВ) жатады, олар иммундық дисрегуляция жағдайында реактивацияға қабілетті.

Зерттеудің мақсаты: COVID-19-бен ауырған науқастарда герпесвирус инфекцияларының (ЦМВ, ЖГВ, ЭББ) реактивациясының клиникалық-эпидемиологиялық ерекшеліктерін симптоматика мен зертханалық мәліметтердің кешенді талдауы негізінде зерттеу.

Әдістер: «Жағдай–бақылау» типіндегі ретроспективті аналитикалық зерттеу жүргізілді. Жалпы 80 пациент қамтылды: олардың 40-ы анамнезінде COVID-19 диагнозы қойылған негізгі топты, ал 40-ы бұрын коронавирус инфекциясын бастан өткермеген бақылау тобын құрады. Статистикалық өңдеу Манн–Уитни критерийі мен Пирсонның χ^2 критерийін қолдану арқылы жүргізілді; $p < 0,05$ мәні статистикалық мәнділік ретінде қабылданды.

Нәтижелер: Зерттеу нәтижесінде герпесвирус инфекцияларының реактивациясы COVID-19-дың орташа және ауыр түрімен ауырған науқастарда жеңіл түрімен ауырғандарға қарағанда жиірек тіркелгені анықталды (75% қарсы 33,3%). Реактивация тобына жататын науқастарда шеткергі лимфаденопатия (85% қарсы 47,5%) және фебрильді қызба (25% қарсы 5%) едәуір жиі кездесті. Серологиялық зерттеу барысында IgG деңгейінің жоғарылауы, оптикалық тығыздықтың артуы және төмен авидтілік анықталды, бұл жасырын вирустың реактивациясын көрсетеді.

Қорытынды: Зерттеу барысында COVID-19-дан кейінгі кезеңде герпесвирус инфекцияларының реактивациясымен байланысты бірқатар клиникалық, эпидемиологиялық және зертханалық ерекшеліктер анықталды. Бұл жағдай SARS-CoV-2 мен латентті вирустардың өзара әрекеттесу мүмкіндігін ескере отырып, постковидтық науқастардың жағдайын кешенді бағалаудың маңыздылығын көрсетеді. Алынған деректер осы бағыттағы әрі қарайғы зерттеулерге негіз бола алады және герпесвирус инфекцияларына скрининг жүргізудің постковидтық мониторинг тәжірибесіне енгізілуінің орынды екенін дәлелдейді.

Түйін сөздер: *постковид синдромы; герпесвирус инфекциялары; қауіп факторлары; COVID-19; вирустардың реактивациясы.*

Дәйексөз үшін:

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Introduction.

COVID-19, caused by the SARS-CoV-2 virus, has emerged as one of the most significant global medical and social challenges of the past decade. Its acute course, along with persistent post-viral inflammation following recovery, contributes to a sustained disruption of immune homeostasis, which may promote the reactivation of latent viruses, including members of the Herpesviridae family [4–6].

Against this background, infections caused by herpesviruses have gained particular relevance, given their prominent role in clinical practice, especially in individuals with underlying immune dysregulation. The latent nature of herpesviruses, their persistence in the host organism, and their ability to reactivate under stressful or immunosuppressive conditions contribute to a wide spectrum of clinical manifestations [1–3].

In recent years, the reactivation of herpesvirus infections following COVID-19 has drawn increasing attention from researchers. According to S.K. Dunmire et al., EBV reactivation may occur as early as the incubation period of COVID-19, triggered by immune restructuring [7]. Similar mechanisms have been observed for CMV, particularly in immunocompromised populations [8–9]. Studies by K. Luzuriaga and J.L. Sullivan emphasize that latent virus reactivation may not only exacerbate the course of the primary illness but also mimic systemic manifestations of COVID-19-associated damage [10].

Post-COVID syndrome is a clinical and pathophysiological condition persisting in a subset of patients after recovery from SARS-CoV-2 infection. It is characterized by a wide range of symptoms, most commonly involving the cardiorespiratory and neuropsychiatric systems, along with signs of immune dysregulation. According to current evidence, the pathogenesis of this condition involves chronic immune activation, cytokine profile dysregulation, the development of autoimmune processes, and functional impairments of epithelial and endothelial cells. Persistent viral components or virus-induced immune surveillance disruption play a crucial role, creating favorable conditions for the reactivation of latent infections, including herpesviruses. These reactivated viruses may, in turn, aggravate the course of post-COVID syndrome by intensifying systemic inflammation and impairing the restoration of immune homeostasis.

Clinical observations have described cases of reactivation of herpes simplex virus, CMV, and EBV following both severe and mild COVID-19 [11–13]. According to several authors, the reactivation of latent viral infections is driven not only by weakened T-cell immune surveillance but also by the direct impact of SARS-CoV-2 on immune cells, including lymphocyte apoptosis and the activation of proinflammatory cytokines [14–15].

Serological studies have demonstrated elevated antibody titers against herpesviruses in patients with post-COVID syndrome, reflecting a reactivation-type immune response, characterized by high-avidity positive IgG and negative IgM [16–17]. Clinically, such patients may report persistent fatigue, sleep disturbances, low-grade fever, and headaches or abdominal pain, complicating differential diagnosis from post-COVID sequelae [18–20].

Despite the abundance of case reports, there is a lack of systematized data on the clinical and epidemiological features of herpesvirus reactivation in patients recovering from COVID-19, particularly in regional populations. This highlights the need for a comprehensive analysis encompassing epidemiological parameters, clinical manifestations, laboratory findings, and immunological markers in this group of patients.

Aim of the Study. To analyze the clinical and epidemiological features of reactivation of chronic herpesvirus infections in patients who have recovered from coronavirus infection.

Objectives

1. To describe the clinical polymorphism and frequency of major complaints associated with herpesvirus reactivation during the post-COVID period.

2. To analyze laboratory and immunological indicators in patients with active herpesvirus infection following COVID-19.

Materials and Methods. This study employed a retrospective analytical observational case–control design aimed at investigating the clinical and epidemiological characteristics of herpesvirus reactivation in patients with a history of coronavirus infection. A total of 80 patients who received treatment between 2021 and 2024 at *City Clinical Hospital No. 7 and the S. Zhekenov City Clinical Infectious Diseases Hospital* (Almaty) were included in the study.

The main group consisted of 40 patients with a confirmed history of COVID-19, diagnosed based on clinical and epidemiological data and confirmed by laboratory testing (PCR and/or serological analysis). The control group included 40 patients with no history of manifest COVID-19, no laboratory confirmation, and no signs indicative of prior SARS-CoV-2 infection. Patient selection was performed through the analysis of medical records, considering epidemiological history, clinical presentation, and laboratory data.

Inclusion criteria encompassed patients aged 18 years and older, with complete medical information regarding COVID-19, as well as available serological and molecular genetic testing data for herpesvirus infections (CMV, EBV, HSV types 1 and 2).

Exclusion criteria included patients with immunodeficiency conditions, malignant neoplasms, ongoing immunosuppressive therapy, and pregnancy.

Depending on the presence of a prior COVID-19 infection and laboratory-confirmed herpesvirus infection, patients were categorized into four groups, including a control group. The control group comprised individuals who had neither COVID-19 nor herpesvirus infection.

In this study, herpesvirus reactivation was determined based on a combination of clinical and laboratory findings. Clinical criteria included the presence of at least three of the following symptoms: low-grade fever, general weakness, malaise, loss of appetite, headache, catarrhal symptoms, skin rashes, joint pain, lymphadenopathy, hepatomegaly, or splenomegaly.

Laboratory signs of reactivation included high titers of specific IgG antibodies with low avidity and/or detection of herpesvirus DNA in biological specimens (blood, saliva, urine) by PCR. Patients meeting at least one laboratory criterion in combination with clinical symptoms were classified as probable cases of latent herpesvirus reactivation.

Statistical analysis was conducted using IBM SPSS Statistics version 26.0. The Mann–Whitney U test was used to assess differences between independent groups. Associations between categorical variables were evaluated using Pearson's chi-square (χ^2) test. A *p-value of <0.05* was considered statistically significant. For key comparisons, 95% confidence intervals and effect sizes were additionally calculated. The analysis addressed variables such as the type of herpesvirus infection, COVID-19 severity, clinical symptom severity, and laboratory parameters. The choice of statistical methods was based on data type and research objectives, adhering to the principles of scientific validity and reproducibility.

Ethical Considerations. The study was conducted in accordance with ethical standards and the principles of the Declaration of Helsinki. The study was approved by the local Ethics Committee of Kazakhstan Medical University "KSPH" (Protocol No. 1 dated January 15, 2024). No personal identifying information was disclosed.

Results.

The study included 80 patients with a mean age of 41.6 years. Women comprised the majority of the sample-63.8% (n = 51), while men accounted for 36.2% (n = 29). The main group consisted of 40 patients with a confirmed history of COVID-19, while the control group included 40 patients (50% of the total sample) without clinical manifestations typical of COVID-19 in their medical history. The distribution of patients based on a history of coronavirus infection was balanced. Among those with a history of SARS-CoV-2 infection, the majority had experienced a mild form of the disease-60% (n = 24). Moderate and severe courses were reported in 20% (n = 8) of cases each (Figure 1).

Among patients with a history of COVID-19, herpesvirus reactivation was observed at a comparable frequency in both females and males, suggesting no significant gender-based association with this phenomenon. However, age-related analysis revealed an increased frequency of reactivation in individuals aged 30–50 years, as well as in those over 60 years of age. These findings may indicate age-dependent variations in immune surveillance over latent viral infections, particularly under conditions of virus-induced immune dysregulation following SARS-CoV-2 infection (Figure 1).

The most pronounced differences between patients with and without reactivation were noted when analyzing the severity of prior COVID-19. Reactivation occurred significantly more often in individuals who experienced moderate to severe forms of COVID-19, whereas cases of reactivation were considerably less frequent among those with mild disease. These data support the hypothesis that intense viral inflammation and immune exhaustion associated with severe COVID-19 may contribute to a loss of immune control over persistent herpesviruses, facilitating their subsequent reactivation.

Among the patients who had previously contracted COVID-19, 60% (24) experienced a mild form of the disease, 20% (8) had a moderate course, and 20% (8) had a severe course. Herpesvirus reactivation was observed in 33.3% (8) of patients with mild COVID-19, in 75% (6) of those with a moderate course, and in 75% (6) of those with a severe course. The overall frequency of herpesvirus reactivation was 50% (20). (Table 1).

A chi-square analysis demonstrated a statistically significant association between the severity of COVID-19 and the frequency of herpesvirus reactivation *($\chi^2 = 6.67$; $p = 0.036$)*. These findings suggest that a more severe course of coronavirus infection may be associated with an increased likelihood of latent virus reactivation, likely due to pronounced immune dysregulation.

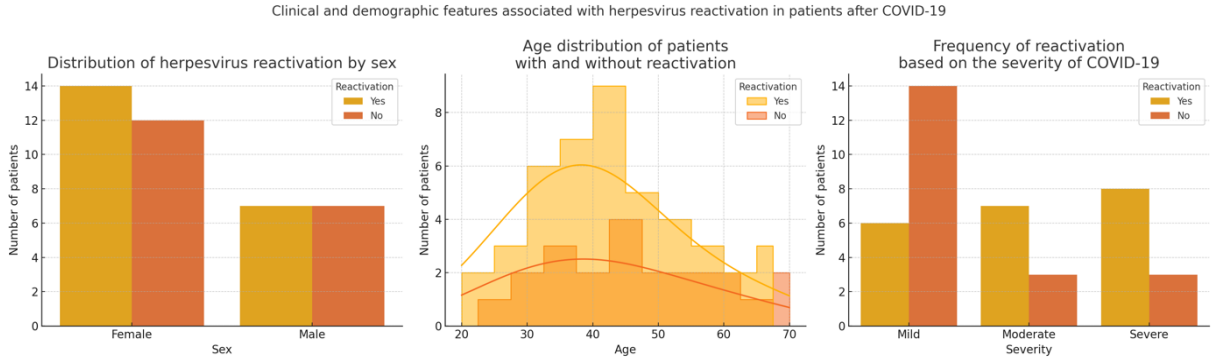

Figure 1. Clinical and demographic features associated with herpesvirus reactivation in patients after COVID-19.

Table 1.

Frequency of herpesvirus reactivation depending on the severity of COVID-19.

COVID-19 Severity	Reactivation Present % (n)	No Reactivation % (n)	Total % (n)
Mild	33,3% (8)	66,7% (16)	60%(24)
Moderate	76% (6)	25% (2)	20%(8)
Severe	76% (6)	25% (2)	20%(8)
Total	50% (20)	50% (20)	100%(40)

Note: $\chi^2 = 6.67$; $p = 0.036$ (Pearson's chi-square test).

When comparing laboratory parameters between patients with and without herpesvirus reactivation using the Mann–Whitney test, statistically significant differences were observed at a significance level of $p < 0.05$. The most pronounced differences were found in the levels of specific antibodies to herpesviruses. For instance, IgG levels to CMV were significantly higher in patients showing signs of reactivation ($p < 0.001$), indicating activation of the humoral

immune response. Similarly, markedly elevated levels of IgG to EBV and HSV types 1 and 2 ($p < 0.001$ *and* $p = 0.001$, respectively) suggest potential activity of latent viral infections during or following COVID-19.

In addition to serological differences, patients with reactivation demonstrated significantly higher levels of C-reactive protein ($p = 0.002$), indicating a systemic inflammatory response. Elevated blood glucose levels ($p = 0.035$) also reached statistical significance, potentially reflecting secondary metabolic disturbances developing in the context of chronic inflammation or viral persistence. (Figure 2).

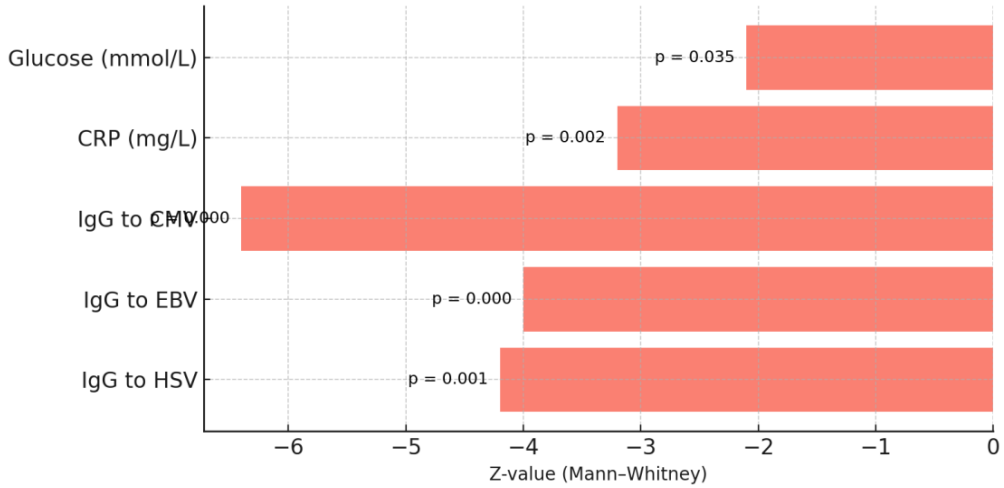

Figure 2. Statistically significant differences in laboratory parameters between patients with and without herpesvirus reactivation.

All reported parameters had p-values below the predetermined threshold of 0.05, supporting the interpretation that these differences are statistically significant and potentially clinically relevant.

A comparative analysis of the frequency of clinical symptoms between patients with herpesvirus reactivation and those without signs of herpesvirus infection revealed marked differences across several parameters. Patients in the reactivation group more frequently reported symptoms such as weakness, malaise, low-grade fever, loss of appetite, headache, and catarrhal manifestations. In addition, this subgroup showed a higher prevalence of skin rashes, lymphadenopathy, joint pain, and signs of hepatomegaly. Complaints related to the cardiovascular and gastrointestinal systems, as well as respiratory symptoms-including cough-were also more common in this group. In contrast, clinical manifestations were significantly less frequent among patients without herpesvirus infection. (Figure 3).

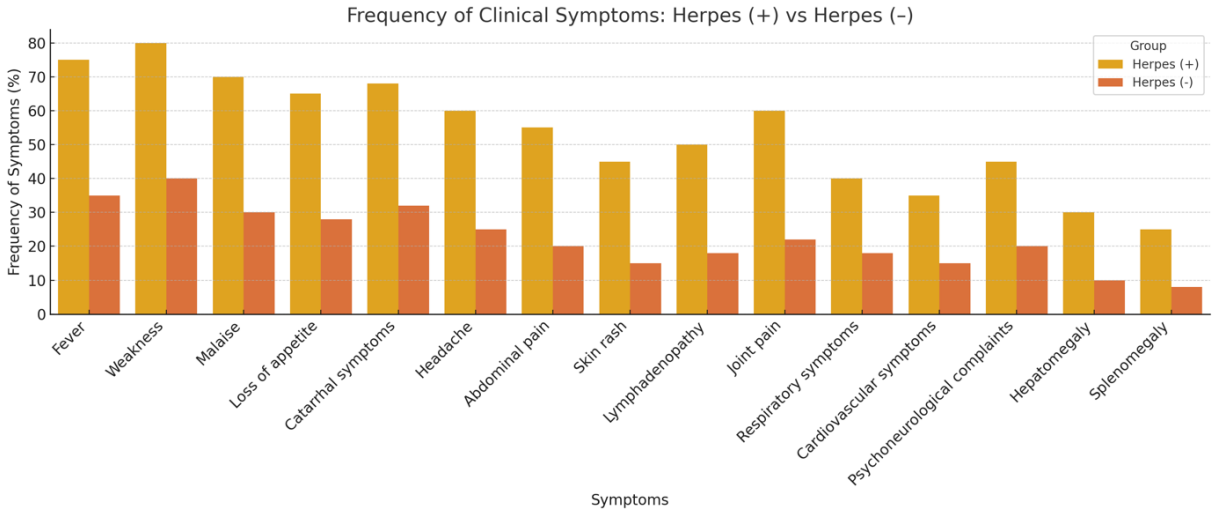

Figure 3. Frequency of clinical symptoms in patients with and without herpesvirus reactivation.

Discussion

The findings of this study underscore the clinical relevance of herpesvirus reactivation in patients with a history of COVID-19. The identified clinical, laboratory, and immunological features point to a strong pathogenetic link between SARS-CoV-2 and herpesviruses-particularly CMV, EBV, and HSV.

The mechanisms underlying herpesvirus activation in the post-COVID period have been discussed in several studies. Immune dysregulation plays a central role, including T-cell apoptosis, reduced antibody avidity, cytokine imbalance, and increased expression of HLA class II molecules [6, 8, 10]. These factors contribute to the

reactivation of latent viruses, enhancing both inflammatory and neurotropic effects [7, 11, 14].

According to S.K. Dunmire and K.A. Hogquist, EBV reactivation frequently occurs even under moderate immunosuppression and may present with nonspecific somatic symptoms such as asthenia, low-grade fever, and myalgia [7]. Similar manifestations were observed in our study among patients with combined COVID-19 and herpesvirus infection, regardless of COVID-19 severity. Epidemiological studies [3, 5, 12] indicate that CMV is the most common herpesvirus reactivation in the context of secondary immunodeficiency. This was confirmed in our analysis: CMV accounted for 30% of all reactivation cases in COVID-positive patients, while EBV and HSV were less frequently detected. In contrast, patients in the control group (without COVID-19) more often exhibited herpesvirus coinfections (e.g., CMV + EBV, CMV + HSV), consistent with previously published findings [1, 15].

Serological profiles of patients indicated predominantly reactivation-type responses-characterized by high titers of specific IgG antibodies with low avidity and/or PCR positivity. These findings align with the results of De Paschale and Clerici, who highlighted the diagnostic value of antibody avidity as a marker of chronic or reactivated infection [16].

Immunologically, patients with herpesvirus reactivation after COVID-19 showed elevated platelet levels, neutrophilic shift, and decreased lymphocyte counts, which support the hypothesis of subclinical inflammation maintained by both residual SARS-CoV-2 activity and reactivated herpesviruses [9, 13, 17].

The polymorphic nature of clinical symptoms observed in this cohort is in agreement with the data presented by James and Kimberlin, who described the systemic but often indolent manifestations of herpesvirus reactivation. The most commonly reported symptoms included low-grade fever, general weakness, reduced productivity, headaches, and muscle pain. In some cases, lymphadenopathy and herpetic rashes on the skin or mucous membranes were also reported. Several patients described sleep disturbances, irritability, and emotional instability. In more pronounced cases, the clinical picture resembled a mononucleosis-like syndrome with pharyngitis and signs of hepatomegaly [11].

Importantly, the results of this study support the hypothesis of a multifactorial nature of post-COVID syndrome, in which herpesviruses act as cofactors that modulate both the duration and intensity of symptoms. According to the work of Luzuriaga and Sullivan,reactivation of latent viruses may play a decisive role in the development of prolonged post-infectious conditions.

The identified features of herpesvirus reactivation in patients recovering from COVID-19 are consistent with previously described mechanisms of viral interaction. These findings highlight the importance of immunological monitoring and support the inclusion of herpesvirus status in the diagnostic and follow-up strategies for individuals with post-COVID syndrome.

Conclusion. This study provides a comprehensive overview of herpesvirus reactivation in patients recovering from COVID-19, revealing significant differences in clinical symptoms, laboratory findings, and serological profiles compared to individuals without prior COVID-19.

Herpesvirus reactivation was more common among COVID-19 survivors, with isolated CMV infections being predominant. In contrast, coinfections involving HSV and EBV were more frequently observed in patients without COVID-19. Clinical symptoms in the reactivation group were more diverse and severe, particularly asthenic, abdominal, and vascular complaints, suggesting a potential contribution of herpesviruses to the persistence or severity of post-COVID syndrome. Laboratory and serological analyses confirmed signs of immune dysregulation and reactivation of latent infections. These findings support the need to include herpesvirus screening in post-COVID care algorithms, even in the absence of overt clinical signs. Further studies on SARS-CoV-2 and Herpesviridae interactions are essential to clarify their role in post-viral pathogenesis and to guide personalized management strategies. This area of research requires continued investigation, particularly in relation to long-term immune alterations, viral persistence, and their implications for clinical outcomes in diverse patient populations.

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