УДК 616.12-008.64-002.2:616.9
https://doi.org/10.20538/1682-0363-2026-2-130-138

Cytomegalovirus Infection Activity as a Predictor of Adverse Clinical Events in Chronic Heart Failure

Shilov S.N.[1], Berezikova E.N.[1], Pankova I.V.[1], Grakova E.V.[2], Kopyeva K.V.[2], Teplyakov A.T.[2], Mayanskaya S.D.[3], Kovalenko G.V.[4], Kolmakova A.M.[4], Kalyuzhin V.V.[4]

[1]*Novosibirsk State Medical University (NSMU)*
52 Krasny Ave., 630091 Novosibirsk, Russian Federation

[2]*Cardiology Research Institute, Tomsk National Research Medical Center (NRMC), Russian Academy of Sciences*
111a Kievskaya St., 634012 Tomsk, Russian Federation

[3]*Kazan State Medical University (KSMU)*
49 Butlerov St., 420012 Kazan, Russian Federation

[4]*Siberian State Medical University*
2 Moskovsky trakt, 634050 Tomsk, Russian Federation

ABSTRACT

Aim. To evaluate the impact of cytomegalovirus (CMV) infection on the course of chronic heart failure (CHF) over a 24-month prospective follow-up.

Material and methods. The study included patients (n = 151) hospitalized due to CHF decompensation. Based on a follow-up, they were divided into groups with favorable and adverse CHF course, underlying pathology, and their complications. The adverse CHF course group included patients who experienced at least one of the following events during the 24-month follow-up period: 1) hospitalization for CHF decompensation; 2) adverse clinical events (cardiovascular death, nonfatal myocardial infarction or acute cerebrovascular accident, and pulmonary embolism); 3) any deterioration in CHF class; 4) a decrease in left ventricular ejection fraction (LVEF) by more than 10% from baseline. Plasma CMV DNA levels were assessed at baseline and after 12 and 24 months of follow-up. To identify predictors of the development of adverse cardiovascular events, ROC analysis was used with the construction of characteristic curves and the calculation of the area under the curve (AUC).

Results. In patients with an adverse CHF course, CMV DNA levels at study inclusion were significantly higher (p < 0.001) compared to those with a favorable CHF course 2,232.0 copies/ml [1,687.0; 2,765.0] and 1,245 copies/ml [991.3; 1,592.0], respectively. The CMV DNA blood plasma level showed a direct correlation with CHF FC (r = 0.66; p = 0.001) and left ventricular end-diastolic dimension (r = 0.53; p = 0.01), while showing a inverse correlation with LVEF (r = –0.49; p = 0.001). The CMV DNA level greater than 1,687 copies/ml predicts adverse cardiovascular events (sensitivity 67%, specificity 81%, AUC = 0.763; p < 0.001) and death (sensitivity 68% and specificity 92%, AUC = 0.844, p < 0.001) in CHF patients over 24 months.

Conclusion. To stratify the risk of developing adverse cardiovascular events during a 24-month follow-up period after CHF decompensation, it is advisable to determine the concentration of cytomegalovirus DNA in the blood of patients with coronary heart disease.

Keywords: cytomegalovirus, herpes virus, heart failure, prognosis, biomarkers

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

✉ *Shilov Sergey N.,* newsib54@gmail.com

Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee of the Novosibirsk Region Municipal Clinical Hospital No. 1 (Minutes No. 200 of January 31, 2019).

For citation: Shilov S.N., Berezikova E.N., Pankova I.V., Grakova E.V., Kopyeva K.V., Teplyakov A.T., Mayanskaya S.D., Kovalenko G.V., Kolmakova A.M., Kalyuzhin V.V. Cytomegalovirus infection activity as a predictor of adverse clinical events in chronic heart failure. *Bulletin of Siberian Medicine.* 2026;25(2):130–138. https://doi.org/10.20538/1682-0363-2026-2-130-138.

Активность цитомегаловирусной инфекции как предиктор неблагоприятных клинических событий при хронической сердечной недостаточности

Шилов С.Н.[1], Березикова Е.Н.[1], Панкова И.В.[1], Гракова Е.В.[2], Копьева К.В.[2], Тепляков А.Т.[2], Маянская С.Д.[3], Коваленко Г.В.[4], Колмакова А.М.[4], Калюжин В.В.[4]

[1] *Новосибирский государственный медицинский университет (НГМУ)*
Россия, 630091, г. Новосибирск, Красный пр., 52

[2] *Научно-исследовательский институт (НИИ) кардиологии, Томский национальный исследовательский медицинский центр (НИМЦ) Российской академии наук*
Россия, 634012, г. Томск, ул. Киевская, 111а

[3] *Казанский государственный медицинский университет (КГМУ)*
Россия, 420012, г. Казань, ул. Бутлерова, 49

[4] *Сибирский государственный медицинский университет (СибГМУ)*
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Цель. Оценить в ходе 24-месячного проспективного исследования влияние цитомегаловирусной (ЦМВ) инфекции на течение хронической сердечной недостаточности (ХСН) у пациентов с ишемической болезнью сердца (ИБС).

Материал и методы. В исследование включены пациенты (n = 151), госпитализированные в связи с ухудшением течения ХСН, которые по результатам наблюдения были разделены на группы с благоприятным и неблагоприятным течением основного заболевания, фоновой патологии и их осложнений. В группу неблагоприятного течения вошли пациенты, у которых в течение 24 мес было зарегистрировано хотя бы одно из указанных событий: 1) госпитализация по поводу декомпенсации ХСН; 2) наступление неблагоприятных клинических событий (сердечно-сосудистая смерть, нефатальный инфаркт миокарда или острое нарушение мозгового кровообращения, тромбоэмболия легочной артерии); 3) любое нарастание функционального класса (ФК) ХСН; 4) уменьшение фракции выброса левого желудочка (ФВ ЛЖ) на 10% и более от исходного значения. Уровень ДНК ЦМВ инфекции в плазме крови оценивали исходно, через 12 и 24 мес наблюдения. Для выявления предикторов развития неблагоприятных сердечно-сосудистых событий использовали ROC-анализ с построением характеристических кривых и расчетом площади под кривой (AUC).

Результаты. У пациентов с неблагоприятным течением ХСН содержание ДНК ЦМВ инфекции в плазме крови на момент включения в исследование было существенно выше (p < 0,001) по сравнению с лицами с благоприятным течением ХСН: 2232,0 [1687,0; 2765,0] и 1245 [991,3; 1592,0] копий/мл соответственно. Уровень ДНК ЦМВ инфекции в плазме крови демонстрировал прямую взаимосвязь со значением ФК ХСН (r = 0,66; p = 0,001), а также с конечно-диастолическим размером левого желудочка (r = 0,53; p = 0,01) и обратную – с ФВ ЛЖ (r = –0,49; p = 0,001). Содержание ДНК ЦМВ инфекции в плазме крови более 1687 копий/мл позволило прогнозировать неблагоприятные сердечно-сосудистые события (чувствительность 67%, специфичность 81%, AUC = 0,763; p < 0,001) и летального исхода (чувствительность 68%, специфичность 92%, AUC = 0,844; p < 0,001) у пациентов с ХСН в течение 24 мес.

Заключение. Для стратификации риска развития неблагоприятных сердечно-сосудистых событий в течение 2 лет после декомпенсации ХСН в крови больных ИБС целесообразно определять концентрацию ДНК ЦМВ инфекции.

Ключевые слова: цитомегаловирус, вирус герпеса, сердечная недостаточность, прогноз, биомаркеры

Для цитирования: Шилов С.Н., Березикова Е.Н., Панкова И.В., Гракова Е.В., Копьева К.В., Тепляков А.Т., Маянская С.Д., Коваленко Г.В., Колмакова А.М., Калюжин В.В. Активность цитомегаловирусной инфекции как предиктор неблагоприятных клинических событий при хронической сердечной недостаточности. *Бюллетень сибирской медицины.* 2026;25(2):130–138. https://doi.org/10.20538/1682-0363-2026-2-130-138.

INTRODUCTION

Despite advances in the fight against coronary heart disease (CHD) thanks to active preventive and therapeutic measures that have led to a reduction in mortality, an alarming trend is observed as an increasing number of patients with CHD are experiencing the development of chronic heart failure (CHF) over time. This, in turn, significantly increases the risk of premature death [1, 2]. This situation makes it extremely important to conduct research aimed at thoroughly understanding the mechanisms of the onset and development of CHF in order to develop innovative and personalized strategies for the prevention of cardiovascular diseases in general, and CHF in particular.

Current concepts regarding the progression of CHF emphasize the role of immune activation and systemic inflammation as key markers of an adverse disease course and high cardiovascular risk [3, 4]. According to this concept, severe microcirculation disorders trigger nonspecific activation of mononuclear cells and monocytes, which triggers the synthesis of proinflammatory cytokines. These cytokines play a crucial role in the evolution of left ventricular dysfunction [5, 6]. It is believed that chronic inflammation can lead to structural changes in cardiomyocytes, including their apoptosis, which ultimately leads to the development of heart failure.

Thus, subclinical cytomegalovirus infection and the accompanying immune response may act as important triggers for the development and decompensation of CHF. This is likely due to the ability of CMV to induce the synthesis of inflammatory markers, such as interleukin (IL) 1β and tumor necrosis factor α (TNFα) [7]. Numerous scientific data obtained from animal experiments, epidemiological and molecular biological studies demonstrate a close association between CMV infection and the aggravation of the atherosclerotic process and the development of acute coronary syndrome (ACS) [8, 9]. Since atherosclerosis and CHD are integral components of the cardiovascular continuum leading to the development of CHF, the need for a detailed study of the influence of CMV on the mechanisms of formation and clinical course of heart failure becomes obvious.

The aim of the study was to analyze the impact of CMV infection on the development and course of CHF in patients with CHD in a 24-month prospective study.

MATERIALS AND METHODS

The study included 151 patients with chronic heart failure (CHF) of ischemic etiology admitted to the Cardiology Unit due to decompensated heart failure. Patients signed an informed consent to participate in the study after resolution of symptoms and signs of CHF decompensation prior to hospital discharge. Patients were then prospectively followed for 24 months. The study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of the State Budgetary Healthcare Institution of the Novosibirsk Region City Clinical Hospital No. 1 (Minutes No. 200 of January 31, 2019).

Exclusion criteria were as follows: acute cardiovascular events in the last six months (cerebrovascular accident, pulmonary embolism, stroke, myocarditis) or the presence of acute myocarditis at onset; heart valve pathology affecting hemodynamics: grade II mitral regurgitation (or higher), aortic stenosis with a pressure gradient > 25 mmHg, grade I aortic insufficiency (or higher), grade II tricuspid regurgitation (or higher); age over 70 years; confirmed COVID-19 (positive PCR test or the presence of IgG to SARS-CoV-2); severe comorbidity: liver disease, end-stage renal failure (glomerular filtration rate (GFR) <30 ml/min/1.73 m²), bronchial asthma or exacerbation of chronic obstructive pulmonary disease; the presence of

autoimmune pathology and malignant neoplasms; lack of informed consent.

Acute coronary syndrome as a reason for hospitalization of patients was excluded based on the absence of clinical, laboratory, and instrumental data (absence of pain syndrome, significant laboratory activity of necrosis markers, characteristic electrocardiographic signs, and the appearance of new zones of impaired local contractility according to echocardiography (EchoCG)) within six months prior to inclusion of patients in the study.

The combined endpoint for the 24-month follow-up period after the first episode of CHF decompensation was the total number of subsequent CHF decompensations requiring hospitalization, as well as major serious adverse events, such as cardiovascular death, nonfatal myocardial infarction, stroke, or pulmonary embolism.

The level of CMV deoxyribonucleic acid (DNA) in blood plasma was determined by the polymerase chain reaction with fluorescence *in situ* hybridization detection of amplification products in real-time mode during hospitalization of patients in the Cardiology Unit due to decompensation of CHF, as well as after 12 and 24 months.

Statistical analysis was performed using R software (version 4.4.3; R Foundation for Statistical Computing, Vienna, Austria). Quantitative variables were presented as minimum (*min*) and maximum (*max*) values, median and interquartile range *Me* [Q_{25}; Q_{75}], and qualitative variables - as absolute and relative *n* (%) frequencies. The prognostic value of parameters was assessed using ROC analysis: models were considered to be adequate if the area under the curve (AUC) was > 0.70. Relationships between features were identified using Spearman's rank correlation. Differences were considered as statistically significant at $p < 0.05$.

RESULTS

After 24 months of follow-up, patients were divided into two cohorts. The first group ($n = 84$) was characterized by an adverse course of the disease. The second group ($n = 67$) included patients with a favorable prognosis. The inclusion criteria in the first group (with an adverse course) were at least one of the following events within 24 months: hospitalization due to decompensated CHF, the development of cardiovascular events (death from cardiovascular causes, nonfatal MI, stroke, and pulmonary embolism), progression of CHF class, or a decrease in left ventricular ejection fraction (LVEF) by 10% or more compared to baseline.

The patient groups were comparable by most of the recorded parameters: gender, age, body mass index, time since the last MI, presence of post-infarction cardiosclerosis, and CHF class (Table 1). However, patients in group 2 were statistically significantly ($p = 0.038$) more likely to have stage 2 CHF compared to patients in group 1 (44.8% vs. 25%, respectively).

The distance measured during the 6-minute walk test at the time of inclusion in the study was significantly lower in group 1 patients compared to group 2 patients ($p = 0.041$), which is consistent with the fact that the number of patients with class 3 CHF was higher among patients with an adverse course of the pathology (68.7% vs. 53.6%). The number of patients seropositive for CMV in group 2 was significantly greater than in group 1 ($p = 0.024$).

Table 1

Clinical and Demographic Characteristics of Patients

Characteristic	Group 1, $n = 84$	Group 2, $n = 67$	p
Gender, male, *n* (%)	55 (65.5)	39 (58.2)	0.455
BMI, kg/m^2, *Me* [Q_{25}; Q_{75}]	30.1 [25.1; 33]	27.7 [24.5; 32.4]	0.146
Age, years, *Me* [Q_{25}; Q_{75}]	57 [52; 63]	59 [55; 63]	0.187
Prior myocardial infarction, *n* (%)	52 (61.9)	44 (65.7)	0.758
Duration of MI, years, *Me* [Q_{25}; Q_{75}]	3.0 [1.5; 4.0]	2.5 [2.0; 4.0]	0.363
CHF stage, *n* (%) Stage 1 Stage 2	 63 (75) 21 (25)	 37 (55.2) 30 (44.8)	0.038
CHF class, *n* (%) Class 2 Class 3	 39 (46.4) 45 (53.6)	 21 (31.3) 46 (68.7)	0.146
6-minute walk test, m, *Me* [Q_{25}; Q_{75}]	289.5 [188.0; 362.0]	233.0 [139.0; 331.5]	0.041
NT-proBNP, pg/ml, *Me* [Q_{25}; Q_{75}]	350.0 [284.0; 526.0]	607.0 [378.5; 920.5]	0.001
LVEF, %, *Me* [Q_{25}; Q_{75}]	44.5 [39.0; 54.8]	41.0 [36.0; 45.5]	0.116
EDD, mm, *Me* [Q_{25}; Q_{75}]	52.0 [49.0; 59.0]	57.0 [54.0; 61.6]	0.042
ESD, mm, *Me* [Q_{25}; Q_{75}]	41.0 [35.8; 47,0]	45.0 [40.0; 49.0]	0.059
Seropositive CMV patients, *n* (%)	34 (40.5)	45 (67.2)	0.024

Note. NT-proBNP – N-terminal pro-brain natriuretic peptide, EDD – end-diastolic dimension, ESD – end-systolic dimension (here and in Table 2).

When comparing CMV-seropositive and -seronegative patients, significant differences in CHF class and stage were revealed (Table 2). Thus, seropositive patients more often had class 3 CHF (70.9% vs. 48.6%, p = 0.042) and stage 2 CHF (41.8% vs. 25.0%, p = 0.043). The results of the 6-minute walk test also demonstrated significant differences: CMV-seropositive patients walked a shorter distance (p = 0.031). Also, CMV-seropositive patients had a significantly higher level of NT-proBNP (p = 0.001).

Table 2

Clinical and Demographic Characteristics of Patient Groups Formed Depending on CMV

Characteristic	CMV –, n = 72	CMV +, n = 79	p
Gender, male, n (%)	43 (59.7)	51 (64.6)	0.395
BMI, kg/m^2, *Me* [Q_{25}; Q_{75}]	30.3 [25.6; 34.4]	27.7 [24.5; 31.9]	0.132
Age, years, *Me* [Q_{25}; Q_{75}]	57.5 [53; 63]	59 [53; 63]	0.262
Prior myocardial infarction, n (%)	45 (62.5)	51 (64.6)	0.911
Duration of MI, years, *Me* [Q_{25}; Q_{75}]	2.5 [2.0; 4.0]	3.0 [2.0; 4.0]	0.489
CHF stage, n (%) Stage 1 Stage 2	 54 (75) 18 (25)	 46 (58.2) 33 (41.8)	0.043
CHF class, n (%) Class 2 Class 3	 37 (51.4) 35 (48.6)	 23 (29.1) 56 (70.9)	0.042
6-minute walk test, m, *Me* [Q_{25}; Q_{75}]	325.5 [208.5; 364.0]	230.0 [136.5; 324.0]	0.031
NT-proBNP, pg/ml, *Me* [Q_{25}; Q_{75}]	350.0 [281.0; 449.0]	580.0 [378.0; 735.5]	0.001
LVEF, %, *Me* [Q_{25}; Q_{75}]	44.0 [38.8; 57.0]	41.0 [37.0; 46.0]	0.095
EDD, mm, *Me* [Q_{25}; Q_{75}]	54.0 [50.0; 59.0]	56.0 [50.5; 61.5]	0.365
ESD, mm, *Me* [Q_{25}; Q_{75}]	41.0 [36.8; 47.0]	45.0 [38.5; 49.0]	0.07

Note. "+" stands for presence; "–" stands for absence

In patients with an adverse course of CHF during 24-month follow-up, the CMV DNA content at the time of inclusion in the study was significantly higher compared to patients who had positive dynamics of the clinical and instrumental characteristics of CHF – 2,232.0 [1,687.0; 2,765.0] copies/ml and 1,245 [991.3; 1,592.0] copies/ml, respectively (p < 0.001) (Fig. 1).

In adverse CHF course, the CMV DNA content did not change significantly, amounting to 2,438.0 copies/ml [1,902.8; 2,847.5] after one year of follow-up (p = 0.115) and 2,218.0 copies/ml [1,845.0; 2,578.5] after two years of follow-up (p = 0.811). In patients with a favorable course of pathology, there was an insignificant decrease in CMV DNA after one year of observation to 1,011.0 copies/ml [697.0; 1,275.5] (p = 0.137), which actually remained at the same level after the next year of observation 1,019.0 copies/ml [799.5; 1,319.0].

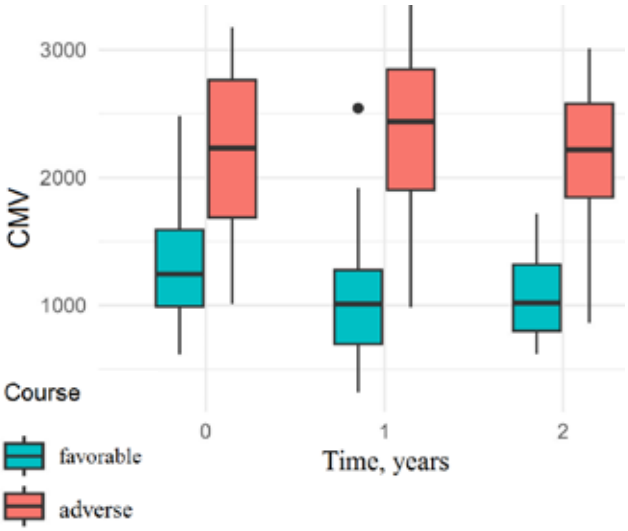
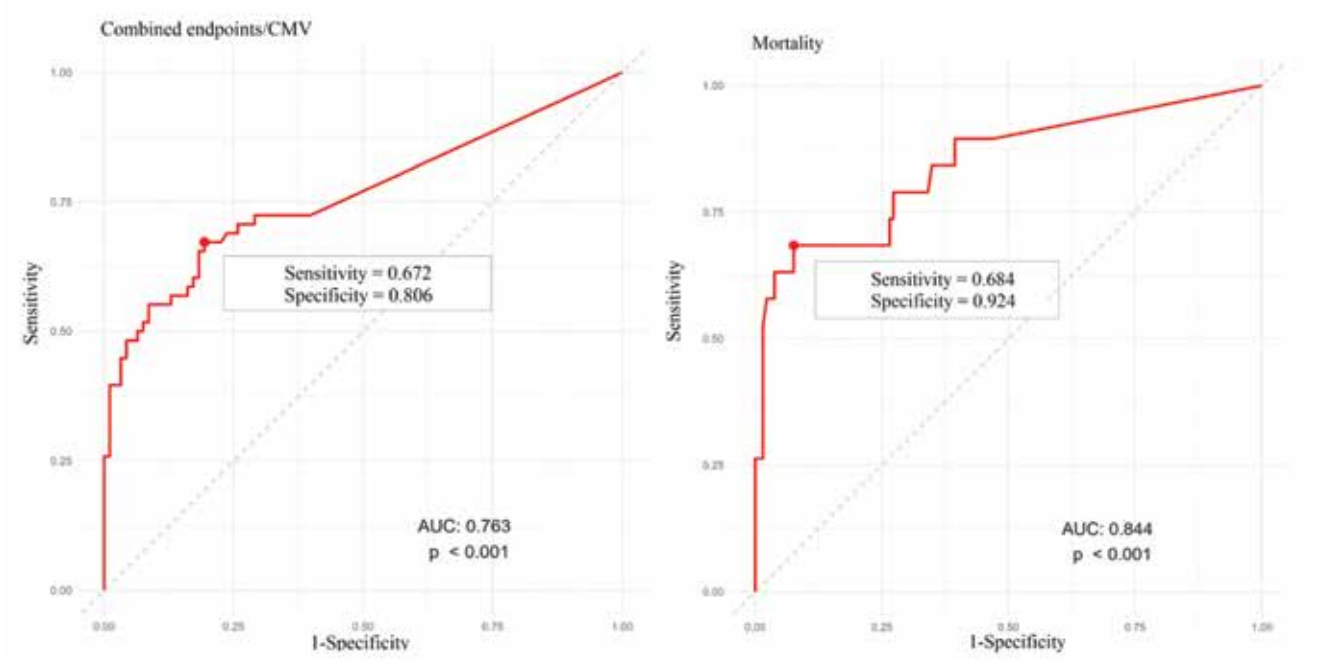


Fig. 1. Dynamics of the CMV DNA content in the blood plasma of patients with favorable and adverse course of CHF, copies/ml: *min* (lower vertical line), Q_{25} (bottom side of the rectangle), *Me* (horizontal line inside the rectangle), Q_{75} (top side of the rectangle), *max* (top vertical line)

Using ROC analysis, it was found that in seropositive patients, the CMV DNA content in blood plasma of more than 1,687 copies/ml allowed for the prediction of adverse cardiovascular events within 2 years after hospitalization for decompensated CHF with sensitivity of 67% and specificity of 81% (AUC = 0.763, p < 0.001) (Fig. 2, *a*). It was also found that the CMV DNA content in blood plasma of more than 1,687 copies/ml allowed for the prediction of death within the next 24 months with a sensitivity of 68% and a specificity of 92% (AUC = 0.844, p < 0.001) (Fig. 2, *b*).

The amount of CMV DNA in blood plasma directly correlated with CHF class (r = 0.66, p = 0.001) and with the EDD (r = 0.53, p = 0.01), and, on the contrary, showed a moderate inverse relationship with the distance covered in the six-minute walk test (r = –0.63, p = 0.001) and LVEF (r = –0.49, p = 0.001) (Table 3).



a *b*

Fig. 2. ROC curves of sensitivity and specificity of CMV DNA level in blood plasma in predicting the development of adverse cardiovascular events (*a*) and mortality (*b*) in CHF patients over 24 months: the area under the curve (AUC) value is presented together with the significance level estimate (*p*)

Table 3

Correlation Analysis of the Relationship between CMV DNA Content and Clinical, Instrumental, and Laboratory Parameters

Parameter	*r*	*p*
CHF class	0.66	0.001
6-minute walk test	–0.63	0.001
LVEF	–0.49	0.01
EDD	0.53	0.01
GFR	0.08	0.73
Total cholesterol	–0.15	0.62
LDL	–0.18	0.6

Note. LDL – low-density lipoprotein, *p* – statistical significance of the correlation coefficient.

DISCUSSION

The data obtained in this study confirm the pathogenetic role of CMV infection in the destabilization of patients with CHF secondary to CHD. The identified correlations between viral load and myocardial structural and functional remodeling indicate a direct link between CMV DNA levels and the risk of adverse cardiovascular events. These results suggest that viral concentration in the blood is a significant factor modulating the severity of heart failure.

Cytomegalovirus establishes deep and complex relationships with the host immune system, resulting in a variety of changes in the functional characteristics of lymphocytes. In immunocompetent individuals, CMV typically manifests as an asymptomatic latent infection with episodic reactivations. In contrast, in immunocompromised patients, it typically causes acute pathology. The host inflammatory response is essential for CMV reactivation and stimulation of its gene expression [10]. Some viral gene products, in turn, induce the host to produce a wide range of proinflammatory cytokines, including tumor necrosis factorα, interleukin-1β, and interleukin-6 [11]. Although CMV reactivation in immunocompromised individuals is associated with severe consequences, it has been established that in elderly patients with CHF, viral reactivation is often subclinical, which complicates timely diagnosis, despite its potential contribution to disease progression [12].

In vivo studies indicate a significant impact of CMV infection on the vascular wall, affecting various cell types. Among the most susceptible cells are monocytes/macrophages, smooth muscle cells, and, most importantly, endothelial cells [13]. The latter play a critical role in maintaining the health of the vascular system. Endothelial cells form the

inner layer of blood vessels, acting as a barrier that regulates vascular wall permeability and controls blood – tissue interactions. They not only passively separate blood from surrounding tissues but also actively participate in the regulation of vascular tone, as if orchestrating vascular processes.

Endothelial cells like a highly organized communication network receive and transmit signals, ensuring the integrity of the vascular system and maintaining normal blood flow. Various biologically active substances synthesized by the endothelium play a key role in this process. Among them are prostacyclin (a potent inhibitor of platelet aggregation), thromboxane A2, which has the opposite effect of stimulating platelet aggregation, endothelin (a regulator of vascular tone), and thrombomodulin, which modulates the blood coagulation system [14]. Thus, endothelial cells maintain a delicate balance between coagulation and fibrinolysis processes, preventing unwanted thrombus formation and maintaining the free flow of blood. In particular, the enzyme adenosine diphosphate (ADP) secreted by platelets plays a significant role in thrombus formation and cellular adhesion, while endothelial cells are actively involved in the regulation of its action [15]. They provide an antithrombotic surface, preventing uncontrolled activation of coagulation factors and platelets. Endothelial dysfunction leads to a chain reaction of pathological processes, triggering an inflammatory process, stimulating the production of cytokines and other inflammatory mediators. This leads to the expression of adhesion molecules on the surface of endothelial cells, which promotes the adhesion of leukocytes to the vessel wall and the further development of inflammation [15].

Studies by Y.J. Tang-Feldman et al. have shed light on the mechanism by which CMV provokes inflammatory processes that can lead to endothelial dysfunction [16]. A key link in this process is the release of arachidonic acid after infection of cells with CMV. This acid, in turn, triggers a cascade of reactions catalyzed by cyclooxygenase (COX). COX activated by early viral proteins IE-72/IE-86 leads to an increase in the production of reactive oxygen species (ROS). An increased concentration of ROS plays a crucial role in the activation of the transcription factor NF-κB, which is located in the cell cytoplasm in an inactive state.

Activation of NF-κB triggers the expression of proinflammatory cytokines, such as IL-6 and IL-8. Further studies by D. Prochnau et al. confirmed a significant increase in the levels of a number of inflammatory factors, including interleukins 6 and 8 and platelet-derived growth factor, in vascular smooth muscle cells 24 and 72 hours after CMV infection [17]. In addition to its direct damaging effect, interleukin 6 also stimulates endothelial cells to release monocyte chemoattractant protein-2 (CCL-2). CCL-2 attracts additional monocytes and lymphocytes to the intima, increasing inflammation in the affected area. Interleukin 8, in turn, activates neutrophils, which, in a process known as an oxidative burst, release a huge amount of ROS. This flow of ROS creates a vicious cycle, further stimulating the production of NF-κB and, consequently, even more inflammatory factors. Ultimately, the interaction of all these factors forms a complex network of interconnected processes, where factors affect each other, exacerbating inflammation and contributing to the development and progression of cardiovascular disease. CMV, through its influence on ROS production and NF-κB activation, plays a key role in this pathological cascade [17, 18], which can ultimately activate inflammation not only in the vascular wall but also in the myocardium, contributing to the progression of cardiac dysfunction.

Our findings confirmed that monitoring CMV viral load in the blood serves as an objective tool for assessing the severity of the condition and predicting the progression of CHF in patients with a history of ischemia. The established direct link between increased viral DNA concentration and the risk of decompensation supports the hypothesis that CMV plays a pathogenic role in the progression of heart failure and the development of adverse cardiovascular outcomes.

Thus, the results of our study highlight the importance of measuring plasma CMV levels for an objective assessment of heart failure severity. This may become an important prognostic test for determining the disease course in patients with coronary heart disease, which, in turn, will optimize the diagnosis and treatment of these patients. Understanding the immune – inflammatory mechanisms underlying ischemic CHF is critical for developing new approaches to studying the pathogenesis of heart failure. These results highlight the importance of developing a comprehensive approach to the prevention and treatment of heart failure that takes into account both infectious and inflammatory mechanisms, which may lead to

improved outcomes in patients with cardiovascular disease.

CONCLUSION

A relationship has been established between plasma CMV DNA concentration and the severity and course of CHF. To stratify the risk of developing adverse cardiovascular events within two years after CHF decompensation, it is advisable to measure plasma CMV DNA concentrations in patients with coronary heart disease.

However, it is important to note that, in our opinion, CMV is not the primary etiologic factor leading to the development of CHF. Patients with pre-existing CHF due to other causes, such as coronary artery disease or hypertension, exhibit decreased immune reactivity. This decrease may be associated with age and the development of systemic circulatory hypoxia, which is also a consequence of CHF. This process results in the activation of latent CMV infection, which, in turn, may lead to further activation of inflammatory processes in the myocardium. Therefore, it can be concluded that the presence of active or latent CMV infection in patients with pre-existing CHF may aggravate the disease and increase the risk of adverse cardiovascular events.

REFERENCES

1. Boytsov S.A. Chronic Heart Failure: Evolution of Etiology, Prevalence and Mortality over the Past 20 Years. *Terapevtichekii Arkhiv.* 2022;94(1):5–8. (In Russ.). DOI: 10.26442/00403660.2022.01.201317.
2. Fomin I.V., Belenkov Yu.N., Mareev V.Yu., Ageev F.T., Artemyeva E.G., Badin Yu.V. et al. EPOCH-CHF As A Mirror of the Current Problems in Cardiovascular Diseases Treatment in Real Clinical Practice. *Kardiologiia*.2024;64(11):48–61. (In Russ.). DOI: 10.18087/cardio.2024.11.n2808.
3. Ageev F.T., Ovchinnikov A.G. Diastolic Heart Failure: 20 Years Later. Current Issues of Pathogenesis, Diagnosis and Treatment of Heart Failure with Preserved LVEF. *Kardiologiia*. 2023;63(3):3–12. (In Russ.). DOI: 10.18087/cardio.2023.3.n2376.
4. Chen J., Zhu Z., Wang Y., Yu J., Zhang X., Xu Y. Cardiac resident macrophages in cardiovascular disease: from physiology to pathology. *Heart.* 2025;111(9):391–400. DOI: 10.1136/heartjnl-2024-324333.
5. Korotaeva a.A., Samoylova E.V., Mindzaev D.R., Nasonova S.N., Zhirov I.V., Tereshchenko S.N. Proinflammatory Cytokines in Chronic Cardiac Failure: State of Problem. *Terapevtichekii Arkhiv.* 2021;93(11):1389–1394. (In Russ.). DOI: 10.26442/00403660.2021.11.201170.
6. Tokmachev R.E., Budnevsky A.V., Kravchenko A.Ya. The Role of Inflammation in the Pathogenesis of Chronic Heart Failure. *Terapevtichekii Arkhiv*. 2016;88(9):106–110. (In Russ.). DOI: 10.17116/terarkh2016889106-110.
7. Cristescu C.V., Alain S., Ruță S.M. The role of CMV infection in primary lesions, development and clinical expression of atherosclerosis. *J. Clin. Med.* 2022;11(13):3832. DOI: 10.3390/jcm11133832.
8. Lebedeva A.M., Maryukhnich E.V., Grivel Zh.Sh., Nikitskaya E.A., Albakova T.M., Albakova R.M. et al. Cytomegalovirus Infection and Endothelial Function in Patients With Acute Myocardial Infarction. *Kardiologiia.* 2018;58(7):41–52. (In Russ.). DOI: 10.18087/cardio.2018.7.10155.
9. Nikitskaya E.A., Grivel Zh.Sh., Maryukhnich E.V., Lebedeva A.M., Ivanova O.I., Savvinova P.P. et al. Cytomegalovirus in Plasma of Acute Coronary Syndrome Patients. *ACTA NATURAE*. 2016;2(29):114–119. (In Russ.). DOI: 10.32607/20758251-2016-8-2-102-107.
10. Griffiths P., Reeves M. Pathogenesis of human cytomegalovirus in the immunocompromised host. *Nat. Rev. Microbiol.* 2021;19(12):759-773. DOI: 10.1038/s41579-021-00582-z.
11. Jackson S.E., Noor M., Lim E., Wills M. The immune response to human cytomegalovirus: impact of age, co-morbidities and the significance of anti-viral activity assessment. *Philos. Trans. R Soc. Lond. B. Biol Sci.* 2025;380(1938):20240408. DOI: 10.1098/rstb.2024.0408.
12. García-Torre A., Bueno-García E., López-Martínez R., Rioseras B., Díaz-Molina B., Lambert J.L. et al. CMV infection is directly related to the inflammatory status in chronic heart failure patients. *Front. Immunol.* 2021;12:687582. DOI: 10.3389/fimmu.2021.687582.
13. Styles J.N., Converse R.R., Griffin S.M., Wade T.J., Klein E., Nylander-French L.A. et al. Human cytomegalovirus infections are associated with elevated biomarkers of vascular injury. *Front. Cell Infect. Microbiol*. 2020;10:334. DOI: 10.3389/fcimb.2020.00334.
14. Yan R., Zhang X., Xu W., Li J., Sun Y., Cui S. et al. ROS-induced endothelial dysfunction in the pathogenesis of atherosclerosis. *Aging Dis*. 2024;16(1):250–268. DOI: 10.14336/AD.2024.0309.
15. Wang X., He B. Endothelial dysfunction: molecular mechanisms and clinical implications. *Med. Comm*. 2024;5(8):e651. DOI: 10.1002/mco2.651.
16. Tang-Feldman Y.J., Lochhead S.R., Lochhead G.R., Yu C., George M., Villablanca A.C. et al. Murine cytomegalovirus (MCMV) infection upregulates P38 MAP kinase in aortas of Apo E KO mice: a molecular mechanism for MCMV-induced acceleration of atherosclerosis. *J. Cardiovasc. Transl. Res*. 2013;6:54–64. DOI: 10.1007/s12265-012-9428-x.
17. Prochnau D., Straube E., Figulla H.R., Rodel J. Supra-additive expression of interleukin-6, interleukin-8 and basic fibroblast growth factor in vascular smooth muscle cells following coinfection with *Chlamydia pneumoniae* and cytomegalovirus as a novel link between infection and atherosclerosis. *Can. J. Infect. Dis. Med. Microbiol*. 2012;23:e26–e30. DOI: 10.1155/2012/987476.
18. Fulkerson H.L., Nogalski M.T., Collins-McMillen D., Yurochko A.D. Overview of human cytomegalovirus pathogenesis. *Methods Mol. Biol*. 2021;2244:1–18. DOI: 10.1007/978-1-0716-1111-1_1.

Author Contribution

Shilov S.N., Pankova I.V., Mayanskaya S.D. – conception and design, data analysis and interpretation, and drafting of the manuscript. Berezikova E.N., Grakova E.V. – conception and design, justification of the manuscript. Kopyeva K.V., Kovalenko G.V., Kolmakova A.M. – data analysis and interpretation. Teplyakov A.T., Kalyuzhin V.V. – final approval of the manuscript for publication.

Author Information

Shilov Sergey N. – Dr. Sci. (Med.), Professor, Department of Pathological Physiology and Clinical Pathological Physiology, NSMU, Novosibirsk, newsib54@gmail.com, http://orcid.org/0000-0002-7777-6419

Berezikova Ekaterina N. – Dr. Sci. (Med.), Professor, Department of Internal Medicine, NSMU, Novosibirsk, cardio@enberezikova.ru, http://orcid.org/0000-0002-9630-0213

Pankova Irina V. – Assistant Professor, Department of Pathological Physiology and Clinical Pathological Physiology, NSMU, Novosibirsk, pankovairin@mail.ru; http://orcid.org/0000-0001-7864-3194

Grakova Elena V. – Dr. Sci. (Med.), Leading Reasercher, Department of Myocardial Pathology, Cardiology Research Institute, Tomsk NRMC, Tomsk, Russian Federation, gev@cardio-tomsk.ru, http://orcid.org/0000-0003-4019-3735

Kopeva Kristina V. – Cand. Sci. (Med.), Senior Researcher, Department of Myocardial Pathology, Cardiology Research Institute, Tomsk NRMC, Tomsk, Kristin-kop@inbox.ru, http://orcid.org/0000-0002-2285-6438

Teplyakov Alexander T. – Dr. Sci. (Med.), Professor, Chief Researcher, Cardiology Research Institute, Tomsk NRMC, Tomsk, Vgelen1970@gmail.com, http://orcid.org/0000-0003-0721-0038

Mayanskaya Svetlana D. – Dr. Sci. (Med.), Professor, Hospital Therapy Department, KSMU, Kazan, smayanskaya@mail.ru, http://orcid.org/0000-0001-6701-5395

Kovalenko GeorgiyV. – 6th-year Student, General Medicine Department, Siberian State Medical University, Tomsk, kovageorgvlad@yandex.ru, http://orcid.org/0009-0005-0070-2111

Kolmakova Arina M. – 6th-year Student, General Medicine Department, Siberian State Medical University, Tomsk, arina.kolmakova.02@mail.ru, http://orcid.org/0009-0008-0480-7094

Kalyuzhin Vadim V. – Dr. Sci. (Med.), Professor, Head of the Advanced Therapy Division with a Course in Rehabilitation, Physiotherapy and Sports Medicine, Siberian State Medical University, Tomsk, kalyuzhinvv@mail.ru, http://orcid.org/0000-0001-9640-2028

(✉) **Shilov Sergey N.,** newsib54@gmail.com

Received on January 23, 2026;
approved after peer review on February 5, 2026;
accepted on February 26, 2026