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ABSTRACT

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LOW HIGH-DENSITY LIPOPROTEIN LEVEL ASSOCIATED WITH ENHANCED INFLAMMATORY RESPONSE AND ONE-YEAR PERSISTENCE OF LONG COVID IN PATIENTS UNDERGOING HEMODIALYSIS: A CROSS-SECTIONAL COHORT STUDY

Background: Long-term consequences of COVID-19, known as long COVID, present distinctive hurdles for patients receiving hemodialysis treatment. Reduced levels of high-density lipoprotein (HDL) (< 1.22 mmol/L) have previously been demonstrated to be associated with heightened susceptibility to COVID-19 and immediate COVID-19-related adverse outcomes in this patient population. However, the potential association between HDL levels and the persistence of long COVID has not been examined within the hemodialysis cohort. The present study aimed to explore the relationship between HDL levels and inflammatory responses one year after COVID-19 among patients undergoing hemodialysis.

Methods: A total of 80 patients treated with hemodialysis, aged 55 (44-62.5) years, with a dialysis vintage of 45 (21-78.6) months and a history of COVID-19, were enrolled in this cross-sectional cohort study. Among them, 45 (56.2%) were diagnosed with long COVID, while 35 (43.8%) had fully recovered. Lipid profiles and inflammatory markers, such as serum C-reactive protein, and interleukins -6 and -17, were assessed one year post-infection.

Results: Patients experiencing long COVID exhibited significantly lower HDL levels compared to fully recovered individuals: 1.19 (1.06-1.76) *vs* 1.66 (1.32-1.92) mmol/L ($p < 0.0001$). The HDL cut-off point of less than 1.22 mmol/L demonstrated a sensitivity of 84.9% and specificity of 95.3% to predict one-year long COVID persistence in our cohort. Among the patients with HDL levels < 1.22 mmol/L, elevated concentrations of C-reactive protein ($p = 0.003$), interleukin-6 ($p = 0.005$), and interleukin-17 ($p < 0.0001$) were evident compared to those with

HDL concentrations exceeding 1.22 mmol/L. Subsequent subgroup analysis revealed a more pronounced inflammatory profile in patients concurrently experiencing long COVID and exhibiting low HDL levels.

Conclusion: The obtained results suggest that a low level of HDL (< 1.22 mmol/L) may exacerbate the inflammatory response in patients undergoing hemodialysis, potentially contributing to the persistence of long COVID even a year after infection. Future research is necessary to elucidate the pathogenetic mechanisms of this relationship and explore potential strategies to improve patient outcomes.

Keywords: long COVID, hemodialysis, high-density lipoproteins, interleukins, inflammation.

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НИЗЬКИЙ РІВЕНЬ ЛІПОПРОТЕЇДІВ ВИСОКОЇ ЩІЛЬНОСТІ АСОЦІЙОВАНИЙ З ПОСИЛЕНОЮ ЗАПАЛЬНОЮ ВІДПОВІДДЮ ТА ПЕРСИСТУВАННЯМ ПОСТКОВІДНОГО СИНДРОМУ ПРОТЯГОМ РОКУ У ПАЦІЄНТІВ, ЯКІ ЛІКУЮТЬСЯ МЕТОДОМ ГЕМОДІАЛІЗУ: ПЕРЕХРЕСНЕ КОГОРТНЕ ДОСЛІДЖЕННЯ

Вступ: Довгострокові наслідки COVID-19, відомі як постковідний синдром, створюють особливі перешкоди для пацієнтів, які лікуються методом гемодіалізу. Продемонстровано, що зниження рівня ліпопротеїдів високої щільності (ЛПВЩ) (< 1,22 ммоль/л) асоціюється з підвищеною сприйнятливістю до COVID-19 і безпосередніми COVID-19-асоційованими несприятливими наслідками в цій категорії пацієнтів. Однак потенційний зв'язок між рівнем ЛПВЩ і постковідним синдромом залишається невизначеним. Метою цього дослідження було вивчити взаємозв'язок між рівнями ЛПВЩ і запальною відповіддю через рік після перенесеної COVID-19 серед пацієнтів, які лікуються методом гемодіалізу.

Методи: 80 пацієнтів, які отримували лікування гемодіалізом та перенесли COVID-19 були включені до цього перехресного когортного дослідження. Середній вік залучених до дослідження пацієнтів склав 55 (44–62,5) років, тривалість діалізної терапії 45 (21–78,6) місяців. Серед них у 45 (56,2%) діагностували постковідний синдром, а 35 (43,8%) повністю одужали. Ліпідні профілі та запальні маркери, такі як сироватковий С-реактивний білок, інтерлейкіни -6 та -17, оцінювали через рік після інфікування COVID-19.

Результати: Пацієнти з постковідним синдромом продемонстрували значно нижчі рівні ЛПВЩ порівняно з особами, які повністю одужали: 1,19 (1,06-1,76) проти 1,66 (1,32–1,92) ммоль/л (p < 0,0001). Пороговий рівень ЛПВЩ менше 1,22 ммоль/л продемонстрував чутливість 84,9 % і специфічність 95,3 % для прогнозування персистенції

постковідного синдрому протягом року у нашій когорті. Серед пацієнтів із рівнем ЛПВЩ < 1,22 ммоль/л спостерігались підвищені концентрації С-реактивного білку крові (p = 0,003), інтерлейкіну-6 (p = 0,005) та інтерлейкіну-17 (p < 0,0001) порівняно з тими, у кого концентрація ЛПВЩ перевищувала 1,22 ммоль/л. Подальший аналіз підгруп виявив статистично значуще підвищення маркерів запалення у хворих, які одночасно мали постковідний синдром та низький рівень ЛПВЩ.

Висновок: Отримані результати свідчать, що низький рівень ЛПВЩ може посилювати запальну реакцію у пацієнтів, які лікуються методом гемодіалізу, потенційно сприяючи персистенції постковідного синдрому навіть через рік після інфікування. Майбутні дослідження необхідні для з'ясування патогенетичних механізмів цього взаємозв'язку та вивчення потенційних стратегій покращення результатів постковідного синдрому у цій когорті пацієнтів.

Ключові слова: постковідний синдром, гемодіаліз, ліпопротеїди високої щільності, інтерлейкіни, запалення.

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INTRODUCTION / ВСТУП

The aftermath of acute SARS-CoV-2 infection has given rise to a complex and multifaceted condition known as long COVID, characterized by persistent symptoms that endure beyond the acute phase of the disease [1, 2]. For individuals undergoing hemodialysis (HD), the challenges posed by long COVID are particularly pronounced, as this patient population already contends with the intricate interplay of renal complications and heightened susceptibility to infections [2–4]. Long COVID was found to be highly prevalent in COVID-19 survivors, representing more than 80% of all cases in the HD population [5, 6]. It has been shown that, during the 90-day post-COVID-19 period, maintenance HD patients who experienced COVID-19 exhibit elevated rates of rehospitalization, respiratory issues, vascular access problems, and higher mortality when compared to HD patients who did not contract COVID-19 [7]. Nonetheless, there is a paucity of studies examining the one-year impact of COVID-19 on HD patients, underscoring the urgency of further research in this area.

Emerging evidence implicates dyslipidemia, particularly low levels of high-density lipoprotein (HDL), is linked to heightened susceptibility to COVID-19, increased cardiovascular risks, elevated infection severity, and higher mortality rates in the general population [8–10]. In addition, our previous report has shown that low HDL levels before the onset of infection are independently associated with COVID-19 morbidity, severity and mortality in patients undergoing HD [11]. However, the association between HDL levels and long-term COVID-19 outcomes in the HD population has never been explored.

HD patients, owing to their compromised immune status and the chronic inflammatory milieu associated with end-stage renal disease, may present unique vulnerabilities to the lingering effects of SARS-CoV-2 infection [12,13]. The presence of comorbidities, including diabetes, hypertension, and cardiovascular disease, further compounds these vulnerabilities [14]. These comorbid conditions, often coexisting with compromised immune function, structural organ disorders, and a pro-inflammatory state, may collectively heighten the susceptibility to and extend the impact of SARS-CoV-2 infection in this particularly vulnerable population [14–16]. Recent research has revealed that reduced levels of HDL are linked to increased levels of the inflammatory marker C-reactive protein (CRP) in COVID-19 patients, suggesting a potential connection between HDL levels and the inflammatory response in the context of long COVID [17]. However, despite the growing recognition of the impact of long COVID on various organ systems, the interplay between HDL levels

and subsequent inflammatory responses in HD patients remains an unexplored area. Therefore, the present study aimed to explore the intricate relationship between HDL levels and the inflammatory response in patients with long COVID undergoing HD one year post-infection.

Materials and Methods

Study Design and Participants. This cross-sectional cohort study was conducted between February 2022 and May 2022 as part of the project "Mechanisms of Development and Therapeutic Targets of Post-COVID Syndrome in Dialysis Patients" (National Study Registration Number 0122U000144) at the State Institution "Institute of Nephrology of the National Academy of Medical Science of Ukraine" in Kyiv, Ukraine. The study protocol received approval from the Institute Ethics Committee (protocol number: 2-2021, dated April 6, 2021), and all participants provided informed consent before inclusion. The research adhered to the principles outlined in the Declaration of Helsinki and other applicable ethical guidelines.

A total of 80 patients undergoing HD who had a documented history of COVID-19 infection were included in the study. Inclusion criteria were an age of >18 years, dialysis treatment of at least 6 months before contracting COVID-19, a clinically stable condition, and an adequately functioning arteriovenous fistula with a target $Kt/V \geq 1.2$. Patients hospitalized in the previous 3 months, or patients with a history of cardiovascular events (angina, myocardial infarction, stroke, heart failure, or peripheral artery diseases requiring hospitalization), immunosuppressive treatment, systemic or malignant diseases, or acute inflammatory processes were excluded. Long COVID was identified by the manifestation of at least one clinical symptom in patients post their COVID-19 infection, with no discernible connection to any other recognized medical condition or disease [1].

Sample Size Determination. The necessary sample size was calculated utilizing G*Power software (version 3.1.9.7), referencing a prior study on cytokine measurement in HD patients post-COVID-19 infection [5]. The study reported effect sizes of 0.81 with sample sizes of 64 for the long-COVID group and 13 for the non-long-COVID group. Based on this effect size (Cohen's $d = 0.81$), an alpha level of 0.05, and a power of 0.80, we determined that a minimum sample size of 34 participants in each group would be essential to detect statistical differences using both the Mann–Whitney test and the ANOVA main effects and interactions test.

Data Collection. One year after SARS-CoV-2 infection, we collected demographic information, routine clinical data, lipid profiles, and inflammatory markers from the participants. Predialysis blood samples were obtained from each individual following an overnight fasting period. Standard biochemical parameters, including blood levels of urea, creatinine, serum albumin, CRP, glucose, and lipid profile components, were assessed using an automatic analyzer "Flexor Junior" (Vital Scientific, Netherlands). Hematological parameters were measured with an "ABX Micros-60" (Horiba Medical, France). Parathyroid hormone (PTH) was evaluated through an immunoradiometric assay, while electrolyte levels were determined using conventional autoanalyzer techniques.

The blood lipid profile included measurements of triglycerides, total cholesterol, HDL cholesterol, and low-density lipoprotein (LDL) cholesterol. The atherogenic index of plasma (AIP) was computed from plasma triglyceride and HDL (log [TG/HDL-C]). Additionally, the body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Interleukin (IL)-6 and IL-17 analysis was carried out using the "SunRise TouchScreen" enzyme and commercially available ELISA kits from IBL International GmbH, Hamburg, Germany. Participants underwent an overnight fast and refrained from strenuous activity for 24 hours before blood collection. Pre-dialysis blood samples (5 mL) were collected, centrifuged at 1500 rpm for 10 minutes to separate plasma/serum, and stored at -20°C until analysis. The cytokine analysis followed the manufacturer's protocol, with samples processed in duplicate.

Statistical Analysis. MedCalc Statistical Software version 20.218 (MedCalc Software Ltd., Ostend, Belgium) was utilized for both statistical analyses and graph generation. Demographic and clinical data were presented as proportions or medians (Me) with interquartile ranges (Q25–Q75) and analyzed using the Chi-squared test (χ^2) or the Mann–Whitney U test, as deemed appropriate. To evaluate the predictive ability of HDL levels for long COVID-19 persistence we performed a Receiver Operating Characteristic (ROC) analysis. The area under the curve (AUC) and optimal cutoff values to maximize sensitivity and specificity were determined. To explore the interaction effects of pre-existing HDL levels and long COVID sequelae on cytokine levels, the Kruskal-Wallis test with the Dunn post-hoc test was implemented.

Results

Patient characteristics. The study included 80 HD patients, with a median age of 55 (44–62.5) years and a dialysis vintage of 45 (21–78.6) months. Among this cohort, 45 patients (56.2%) experienced persistent long COVID sequelae, while 35 patients (43.8%) had fully recovered one year after the onset of acute COVID-19. **Table 1** displays the patient characteristics categorized based on the presence or absence of long COVID one year after infection.

Table 1 – Patient characteristics stratified by the persistence of long COVID one year after infection

	Long COVID group (n = 45)	**Long COVID-free group (n = 35)**	***p*-value**
Male gender, n (%)	28 (62.2%)	17 (48.6%)	0.23
Age, years	56 (44–62)	55 (45–64)	0.98
Dialysis vintage, years	4.2 (3.4–9.7)	3.3 (3.1–7.2)	0.51
BMI, kg/m^2	28.9 (24.2–31.3)	25.6 (23.3–29.8)	0.05
Kt/V	1.3 (1.3–1.4)	1.4 (1.3–1.5)	0.003
Systolic blood pressure, mm Hg	145 (140–160)	120 (117.5–130)	< 0.0001
Diastolic blood pressure, mm Hg	85 (80–95)	70 (60–80)	< 0.0001
Hb, g/L	98.4 (91.2–117)	107 (94.2–113)	0.57
Serum albumin, g/L	36.9 (35.5–40.7)	38.5 (36.1–41.6)	0.02
Calcium, mmol/L	2.32 (2.22–2.36)	2.31 (2.24–2.40)	0.62
Phosphorus, mmol/L	1.75 (1.35–1.92)	1.51 (1.25–2.15)	0.59
iPTH, ng/L	168 (77.4–656.7)	150 (110–389)	0.59
Ferritin (ng/ml)	322 (135.5–401)	303 (159.3–376.5)	0.21
Total cholesterol, mmol/L	4.9 (4.2–5.6)	4.7 (4.4–5.2)	0.76
Triglycerides, mmol/L	1.57 (1.1–2.5)	1.12 (0.9–1.7)	0.06
LDL, mmol/L	3.2 (2.5–3.6)	2.3 (1.5–2.9)	0.05
HDL, mmol/L	1.19 (1.06 –1.76)	1.66 (1.32–1.92)	< 0.0001
AIP	3.2 (2.5–4.9)	2.7 (1.9–3.1)	0.01

Abbreviation: AIP – atherogenic index of plasma, BMI – body mass index, Hb – hemoglobin, HDL – high-density lipoproteins, iPTH – intact parathyroid hormone, LDL – low-density lipoproteins

As depicted in Table 1, individuals experiencing long COVID demonstrated elevated blood pressure, BMI, low-density lipoproteins (LDL) levels, and atherogenic index of plasma compared to those without long COVID. Additionally, they manifested lower levels of serum albumin, hemoglobin (Hb), calcium, and HDL concentrations.

HDL levels and one-year long COVID persistence. The ROC analysis was employed to discern the predictive accuracy of specific HDL cut-off points to predict long-term COVID-19 persistence. We found that the HDL cut-off point of less than 1.22 mmol/L demonstrated a sensitivity of 84.9% and specificity of 95.3% (**Fig. 1**). Patients with HDL levels below 1.22 mmol/L exhibited a notably higher prevalence of long-term COVID-19 sequelae in a year after infection contrasted with those having HDL concentrations of 1.22 mmol/L or greater ($\chi^2 = 63.8$, $p < 0.0001$).

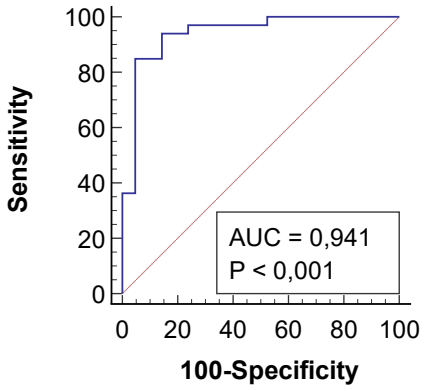

Figure 1 – ROC analysis for prediction of one-year long COVID-19 persistence using HDL levels in patients undergoing HD

HDL levels and inflammatory markers. Among participants with HDL levels < 1.22 mmol/L, we observed elevated concentrations of inflammatory markers compared to those with HDL concentrations exceeding 1.2 mmol/L (**Fig. 2**). Specifically, patients with low HDL levels exhibited higher levels of CRP, interleukin-6 (IL-6), and interleukin-17 (IL-17), indicating an intensified inflammatory response. Subsequent subgroup analysis focused on patients concurrently experiencing long COVID and exhibiting low HDL levels. This subgroup displayed a significant elevation of CRP, IL-6, and IL-17 concentrations, highlighting a potential synergistic effect between long COVID and low HDL in promoting heightened inflammation (**Fig. 3**).

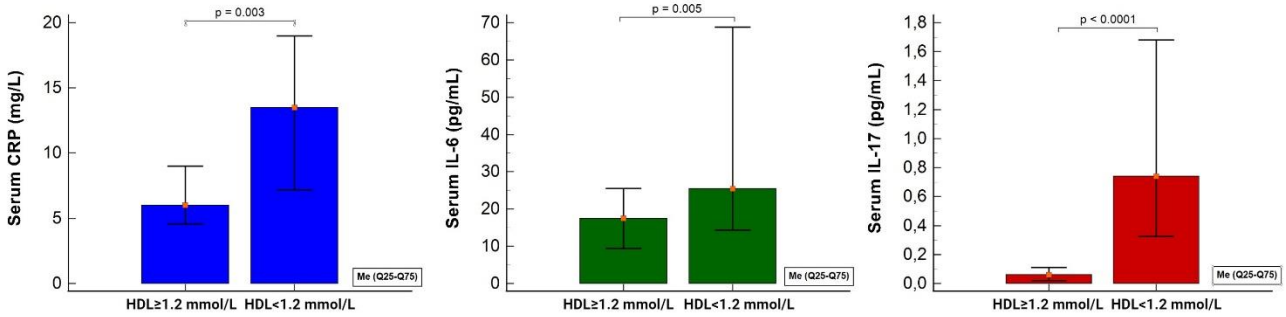

Figure 2 – Serum CRP, IL-6, and IL-17 levels in patients undergoing HD stratified by HDL levels one year after COVID-19

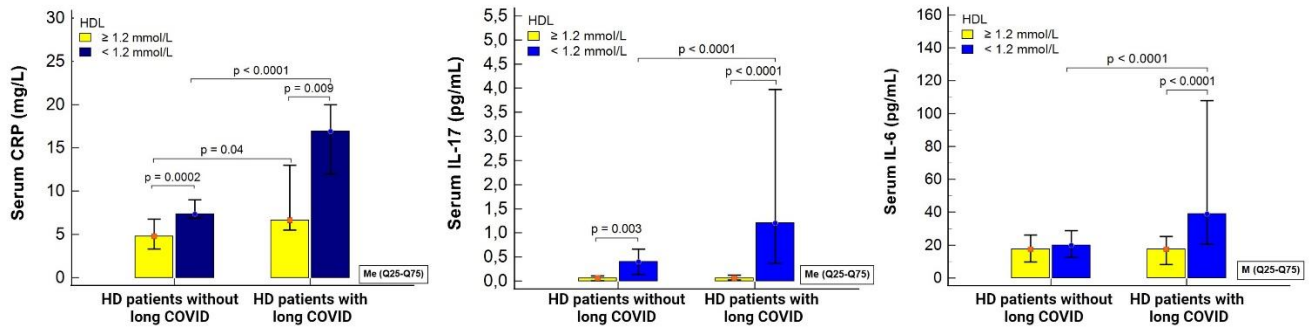

Figure 3 – Serum levels of CRP, IL-6, and IL-17 stratified according to long COVID persistence and HL concentrations one year after COVID-19

Discussion

We established a noteworthy association, revealing that HDL levels below 1.22 mmol/L are linked to the persistence of long COVID one year after infection, accompanied by a heightened inflammatory response in HD patients. This is evidenced by significantly increased concentrations of CRP, IL-6, and IL-17, suggesting a potential link between HDL status and the inflammatory response. The observed association between low HDL levels and an augmented inflammatory response in HD patients with long COVID underscores the intricate interplay between dyslipidemia, chronic inflammation, and the lingering effects of SARS-CoV-2 infection. The significant decrease in HDL levels observed in HD patients with long COVID is consistent with prior research in the general population, emphasizing the influence of COVID-19 on lipid metabolism [8–10]. Similar results were reported in the HD population evaluating the impact of pre-existing HDL levels and immediate COVID-19 outcomes [11].

The inflammatory milieu associated with long COVID has been a subject of growing concern, and

our findings suggest that patients undergoing HD may be particularly vulnerable to sustained inflammatory responses. HD patients already contend with chronic low-grade inflammation, and the addition of SARS-CoV-2 infection may exacerbate this condition, contributing to long COVID persistence [7,12,15]. The subgroup analysis further emphasizes the synergistic effect of long COVID and low HDL levels on inflammation, suggesting a potential dual-hit hypothesis where these factors act in concert to amplify the inflammatory cascade. The "dual-hit" hypothesis, which has been proposed in the context of COVID-19, suggests that the combination of two factors, such as viral infection and another environmental or biological influence, may have a synergistic effect on disease severity or outcomes [18].

Our findings prompt further exploration into the potential mechanisms underlying the association between low HDL levels and heightened inflammation. HDL is known for its anti-inflammatory and antioxidant properties and its role in cholesterol efflux, which is the process of removing excess cholesterol from cells, including immune cells [19, 20]. In the context of long COVID persistent low HDL levels may lead to a dysregulated immune response, resulting in an amplified and prolonged inflammatory state. This is because HDL modulates the function of immune cells and inhibits the production of pro-inflammatory cytokines [17,20]. When HDL levels are low, cholesterol can build up within immune cells, potentially triggering inflammatory pathways and contributing to an exaggerated inflammatory response [19]. This dysregulation may be particularly pronounced in long COVID, where the immune system is dealing with persistent viral effects. HDL also plays a crucial role in maintaining vascular homeostasis and modulating endothelial function [21,22]. Endothelial dysfunction is recognized as a central factor in COVID-19 progression and long COVID [23]. In patients with long COVID, compromised HDL levels may contribute to endothelial dysfunction and vascular inflammation, further exacerbating the inflammatory milieu [9,20].

The implications of our findings extend beyond the immediate context of long COVID, emphasizing the importance of monitoring lipid profiles in HD patients recovering from COVID-19. Both reduced and very high HDL levels have been consistently associated with an increased risk of cardiovascular disease [24,25]. Low HDL levels observed in long COVID patients may, therefore, enhance their susceptibility to cardiovascular complications [26]. Recognizing the connection between changes in lipid profiles and cardiovascular risk underscores the importance of thorough, long-term cardiovascular monitoring and management in individuals recovering from COVID-19, particularly those with compromised kidney function and low HDL levels [27]. Strategies to raise HDL levels or modulate inflammatory responses may be potential avenues for intervention, but further research is essential to delineate the most effective approaches.

Limitations of this study include its cross-sectional nature, which precludes the establishment of causal relationships. Additionally, the relatively small sample size necessitates caution in generalizing the findings to broader populations. Longitudinal studies with larger cohorts are warranted to validate our observations and provide a more nuanced understanding of the dynamics between long COVID, HDL levels, and inflammation.

CONCLUSIONS / ВИСНОВКИ

Together, our study provides valuable insights into the association between low HDL levels, elevated levels of CRP, IL-6, and IL-17, and the lingering effects of COVID-19 in HD patients. The findings indicate that low HDL levels (< 1.22 mmol/L) might exacerbate the inflammatory response in HD patients, potentially leading to the prolonged persistence of long COVID even one year after infection. Further research is essential to uncover the underlying pathogenetic mechanisms of this association and to explore potential strategies for enhancing outcomes in HD patients with long COVID.

PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Our study's findings suggest several directions for future research. First, there is a need for in-depth investigations to uncover the molecular mechanisms by which low HDL levels contribute to heightened inflammation and prolonged COVID-19 effects in patients with heart disease. Second, it is essential to conduct longitudinal studies to understand the temporal dynamics of HDL levels, inflammatory responses, and the persistence of COVID-19 effects over an extended period. Additionally, further research should explore the specific cardiovascular outcomes associated with altered HDL levels in long COVID patients undergoing hemodialysis, including the incidence of cardiovascular

events, progression of atherosclerosis, and overall cardiovascular mortality in this vulnerable population. Furthermore, the development of risk stratification models that incorporate HDL levels, inflammatory markers, and other relevant clinical parameters can aid in identifying heart disease patients at higher risk for persistent COVID-19 effects and cardiovascular complications. Lastly, evaluating the impact of interventions designed to improve HDL levels on long-term outcomes, such as inflammation, cardiovascular events, and overall survival, will be crucial in informing evidence-based clinical practices for heart disease patients recovering from COVID-19.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

N.S.: Conceptualization, formal analysis, original draft preparation; V.D.: Methodology, review, and editing; A.R. and L.S.: Data curation; M.K.: Project management. All the authors reviewed the manuscript and approved it for publication.

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