 УДК 616.12-036.21-092.9:578.834

LONG-TERM CARDIOVASCULAR OUTCOMES IN COVID-19 SURVIVORS: INSIGHTS INTO PREDICTORS AND BIOMARKERS

A. Hovornyan, T. Ilashchuk

Bukovinian State Medical University, Chernivtsi, Ukraine

The COVID-19 pandemic has left a significant burden of long-term health complications, particularly in the cardiovascular domain. Understanding the predictors and mechanisms underlying these complications is crucial for improving post-COVID-19 care and outcomes.

***Objective** – to evaluate long-term cardiovascular (CV) outcomes in COVID-19 survivors, identify key biomarkers and predictors, and develop predictive models for risk stratification.*

***Materials and Methods**. The study included 328 hospitalized patients diagnosed with COVID-19 and moderate to severe viral pneumonia who were followed for 12 months after discharge. Exclusion criteria included in-hospital mortality, previous cardiovascular events (such as myocardial infarction or stroke), and severe chronic comorbidities. The cohort comprised men and women aged 42-71 years. Following the observation period, patients were divided into two groups: those who developed cardiovascular complications and those without such outcomes. Clinical, laboratory, and instrumental parameters – including biomarkers such as C-reactive protein (CRP), D-dimer, and neutrophil-to-lymphocyte ratio (NLR) – were comprehensively analyzed. Statistical analysis included descriptive statistics, Student's t-test for continuous variables, chi-squared tests for categorical data, logistic regression to identify independent predictors, and Receiver Operating Characteristic (ROC) analysis with Area Under the Curve (AUC) to evaluate model performance. Data preprocessing involved standardization of continuous variables and exclusion of incomplete records. Analyses were conducted using Python and Google Sheets, with $p < 0.05$ considered statistically significant. The study was approved by the Bioethics Committee of Bukovinian State Medical University (Protocol No. 1, September 15, 2022) and performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before inclusion.*

***Results**. During follow-up, 31.4% of patients developed cardiovascular complications, including arrhythmias (5.2%), myocardial infarction (8.2%), and MACE (16.5%). Male sex and age were significant demographic predictors of CV outcomes (OR = 1.95 and OR = 1.04 per year, respectively). Biomarker analysis revealed significantly higher levels of NLR and D-dimer in patients with CV complications ($p < 0.001$). NLR emerged as the strongest individual predictor with an odds ratio of 18.18 and an AUC of 0.72. Predictive models combining biomarkers and demographic factors achieved an AUC of 0.93 for CV complications, demonstrating enhanced performance over individual predictors.*

***Conclusions**. 1. COVID-19 survivors show a high prevalence of long-term cardiovascular complications, including MACE, arrhythmias, and myocardial infarction. 2. Elevated NLR and D-dimer levels are key predictors of adverse cardiovascular outcomes. 3. Predictive models integrating biomarkers improve risk assessment and patient stratification. 4. Comprehensive post-COVID care requires routine cardiovascular screening and multidisciplinary management. 5. Long-term cardiovascular monitoring and predictive frameworks are essential for improving outcomes and healthcare resilience.*

***Key words:** COVID-19, cardiovascular outcomes, risk factors, prognostic models, prediction.*

Clinical and experimental pathology 2025. Vol. 24, № 3 (93). P. 55-63.

DOI 10.24061/1727-4338.XXIV.3.93.2025.08

E-mail: *anastasiia.hv@bsmu.edu.ua*

ВІДДАЛЕНІ СЕРЦЕВО-СУДИННІ НАСЛІДКИ У ПАЦІЄНТІВ, ЯКІ ПЕРЕНЕСЛИ COVID-19: АНАЛІЗ ПРЕДИКТОРІВ ТА БІОМАРКЕРІВ

А.В. Говорнян, Т.О. Ілащук

Буковинський державний медичний університет, Чернівці, Україна

Пандемія COVID-19 спричинила значне навантаження у вигляді довготривалих ускладнень для здоров'я, особливо в серцево-судинній сфері. Розуміння предикторів і механізмів, що лежать в основі цих ускладнень, є критично важливим для покращення догляду за пацієнтами після COVID-19 та їхніх

***Ключові слова**: COVID-19, серцево-судинні наслідки, фактори ризику, прогностичні моделі, прогнозування.*

клінічних результатів.
***Мета роботи** – оцінити довготривалі серцево-судинні (СС) наслідки у пацієнтів, які перенесли COVID-19, визначити ключові біомаркери та предиктори, а також розробити прогностичні моделі для стратифікації ризику.*
***Матеріали і методи.** У дослідження включено 328 госпіталізованих пацієнтів із підтвердженим COVID-19 і пневмонією середнього або тяжкого перебігу, яких спостерігали протягом 12-ти місяців після виписки. Критеріями виключення були летальні випадки під час госпіталізації, наявність в анамнезі серцево-судинних подій (інфаркт міокарда, інсульт) та тяжких декомпенсованих супутніх захворювань. До вибірки увійшли чоловіки та жінки віком 42-71 років (середній вік 56,6 ± 0,5 року). Після періоду спостереження пацієнтів поділено на дві групи: із серцево-судинними ускладненнями та без них. Проаналізовано клінічні, лабораторні й інструментальні показники, зокрема С-реактивний білок (CRP), D-димер та співвідношення нейтрофілів до лімфоцитів (NLR). Статистичний аналіз включав описову статистику, t-тест Стьюдента для кількісних змінних, критерій χ^2 для категоріальних показників, логістичну регресію для виявлення незалежних предикторів та ROC-аналіз із розрахунком площі під кривою (AUC) для оцінки точності прогностичних моделей. Попередньо проводили стандартизацію кількісних змінних і виключення неповних записів. Аналіз виконували з використанням Python та Google Sheets; статистично значущими вважалися результати при $p < 0,05$. Дослідження схвалене Комісією з біоетики Буковинського державного медичного університету (Протокол № 1 від 15.09.2022) та проведене відповідно до Гельсінської Декларації. Перед включенням до дослідження всі учасники надали письмову інформовану згоду.*
***Результати.** Протягом періоду спостереження у 31,4% пацієнтів виявлено серцево-судинні ускладнення, зокрема аритмії (5,2%), інфаркт міокарда (8,2%) та MACE (16,5%). Чоловіча стать і вік були значущими демографічними предикторами СС-наслідків (ВШ = 1,95 та ВШ = 1,04 на рік відповідно). Аналіз біомаркерів показав суттєво вищі рівні NLR і D-димеру в пацієнтів із СС-ускладненнями ($p < 0,001$). NLR виявився найпотужнішим індивідуальним предиктором (ВШ = 18,18; AUC = 0,72). Прогностичні моделі, що поєднували біомаркери та демографічні чинники, досягли AUC = 0,93 для СС-ускладнень, що засвідчує про значно вищу ефективність порівняно з окремими предикторами.*
***Висновки.** 1. У пацієнтів після COVID-19 відзначається висока частота віддалених серцево-судинних ускладнень, зокрема MACE, аритмій та інфаркту міокарда. 2. Підвищені рівні NLR та D-димеру є ключовими предикторами несприятливих серцево-судинних подій. 3. Використання предиктивних моделей із включенням біомаркерів покращує оцінку ризику та стратифікацію пацієнтів. 4. Комплексна постковідна допомога потребує регулярного кардіологічного скринінгу та мультидисциплінарного підходу. 5. Довгостроковий кардіологічний моніторинг і предиктивні підходи є ключовими для поліпшення результатів лікування та стійкості системи охорони здоров'я.*

Клінічна та експериментальна патологія 2025. Т.24, № 3 (93). С. 55-63.

Introduction

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has resulted in an unprecedented global health crisis with widespread ramifications. While significant efforts have been directed toward managing acute COVID-19 infections, the long-term complications in survivors are becoming a major area of concern. Among these, cardiovascular disorders have emerged as critical sequelae, contributing to increased morbidity and mortality in the post-acute phase of the disease. The evolving understanding of these complications underscores the necessity of identifying reliable markers and predictors to guide prevention, early detection, and intervention strategies [1, 2].

Evidence indicates that SARS-CoV-2 infection can trigger both direct and indirect damage to the cardiovascular system. Direct effects include myocardial injury caused by viral invasion and inflammation, while indirect mechanisms involve systemic responses such as cytokine storms, endothelial dysfunction, and hypercoagulability [2, 3]. These processes may lead to a spectrum of cardiovascular outcomes, including myocardial infarction, cerebrovascular events, arrhythmias, and pulmonary embolism [3]. Furthermore, studies suggest that chronic inflammation and immune dysregulation play pivotal roles in driving these complications, even months after the resolution of the acute infection [1, 4].

Despite significant advances in understanding COVID-19's cardiovascular impacts, there remains a lack of standardized methods to predict long-term outcomes. Traditional clinical parameters, such as elevated levels of inflammatory markers and hematological indices, have shown potential as predictors of cardiovascular risk. However, the integration of these markers into a comprehensive predictive framework remains underexplored [3, 5]. Identifying and validating these markers can not only enhance individualized risk

stratification but also pave the way for targeted therapeutic interventions [4, 5].

To address these gaps, this study investigates key markers and predictors of cardiovascular outcomes in COVID-19 survivors. By analyzing longitudinal clinical, laboratory, and instrumental data, we aim to identify specific factors associated with adverse cardiovascular events. The insights gained from this research could inform clinical practice and policy by providing evidence-based strategies for long-term cardiovascular care in COVID-19 survivors.

The aim of the work

To evaluate long-term cardiovascular outcomes in COVID-19 survivors, identify key biomarkers and predictors, and develop predictive models for risk stratification.

Research materials and methods

This study included 328 COVID-19 patients who were admitted to the hospital with pneumonia and had a moderate to severe course of the disease. Specifically, exclusion criteria included:

- In-hospital mortality;
- History of cardiovascular events, including myocardial infarction, stroke etc.;
- Severe chronic comorbidities, such as decompensated heart failure, chronic kidney disease stages IV-V, active malignancies, or chronic liver failure.

Following discharge, patients were monitored for a 12-month period.

The obtained data encompassed a comprehensive set of clinical information, laboratory and instrumental investigation results, and medical records collected during the follow-up period. For laboratory biomarkers, if a marker was measured multiple times, the highest result for each patient was considered in the analysis to ensure identification of peak levels.

The study population included both male and female participants, with ages ranging from 42 to 71 years (Fig. 1). The mean age of the population was 56.58 ± 0.50 years. When stratified by gender, the mean age of males was 56.77 ± 0.70 years, while that of females was 56.38 ± 0.72 years. A two-sample t-test revealed no statistically significant difference in the average ages between genders (p = 0.6994).

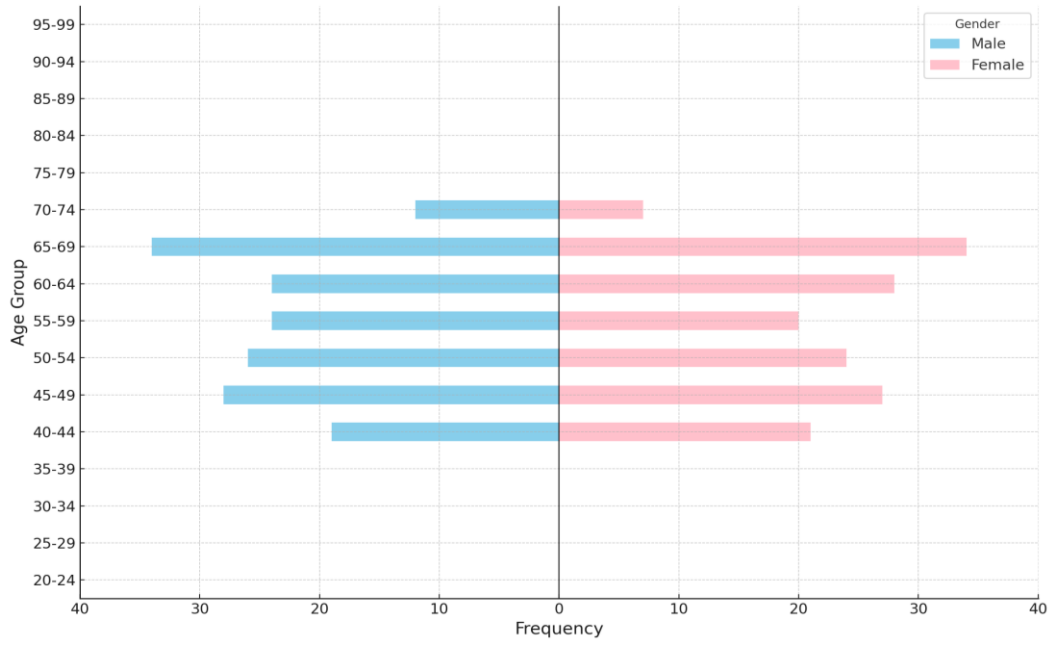

Fig. 1. The demographic characteristics of studied population

The gender distribution of the cohort was as follows: 162 (49.4%) men and 166 (50.6%) women. These findings are illustrated in Figure 1, which provides a histogram of the age and sex distribution.

Descriptive statistics were used to summarize the demographic, clinical, and laboratory characteristics of the study cohort. Continuous variables were expressed as mean ± standard error of the mean (SEM), and categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using independent t-tests for continuous variables and chi-squared tests for categorical variables. For laboratory biomarkers, comparisons of levels between groups with and without cardiovascular (CV) outcomes were analyzed. Biomarkers showing significant differences were further evaluated for their predictive potential using logistic regression analysis.

The statistical analysis aimed to evaluate the predictive value of various clinical markers and demographic variables for cardiovascular (CV) complications and Major Adverse Cardiovascular Events (MACE). Data preprocessing included standardization of continuous variables and handling of missing values by excluding incomplete records from the respective analyses.

Receiver Operating Characteristic (ROC) curve analysis was performed to assess the predictive performance of individual variables and combinations of variables. The Area Under the Curve (AUC) was calculated for each model to quantify its discriminatory

power. AUC values range from 0.5 (no discrimination) to 1.0 (perfect discrimination).

Logistic regression models were used to combine predictors, including age, sex, diabetes status, and biomarkers such as C-reactive protein (CRP), D-Dimer, and neutrophil-to-lymphocyte ratio (NLR). Predictor variables were standardized before inclusion in the regression models to ensure comparability. The probabilities derived from logistic regression were used to generate ROC curves for combined models.

Comparative analyses included:

- Individual predictors (e.g., age, sex, CRP, D-Dimer, NLR) for their standalone predictive performance.
- Combined predictors (e.g., age + sex, biomarkers + diabetes) to evaluate the incremental predictive value.

Results are presented as ROC curves with AUC values for each predictive model, highlighting the relative contributions of individual and combined predictors in distinguishing between patient outcomes.

All statistical analyses were performed using Google Sheets and Python. A p-value < 0.05 was considered statistically significant.

The study was carried out within the framework of the research project «Comorbidity in internal medicine: features of disease course, diagnostic approaches using artificial intelligence, and preventive strategies in the era of global challenges» (State Registration №0125U001449).

The study was conducted in accordance with the basic principles of the World Medical Association Declaration of Helsinki regarding ethical principles for medical research involving human participants. The study protocol was reviewed and approved by the Bioethics Committee of Bukovinian State Medical University (Protocol № 1, dated September 15, 2022). All participants provided written informed consent prior to inclusion in the study.

Results and their discussion

The analysis of cardiovascular (CV) outcomes revealed diverse findings. Arrhythmias were observed in 5.2% of participants, with 6 cases reported in females and 11 in males. Cardiomyopathy was rare, affecting only 0.6% of the cohort. First-time hypertension was noted in 4.6% of individuals, comprising 4 cases in females and 11 in males. Heart failure was present in 2.1% of the population, with 3 cases in females and 4 in males. Myocarditis affected 2.4% of individuals, evenly distributed between the genders with 4 cases each. The most common complication was major adverse cardiovascular events (MACE), affecting 54 people (16.46%). The majority of patients (68.6%) did not experience any CV complications, with 122 cases in females and 103 in males. The chi-square test was used to compare the distribution of cardiovascular outcomes between males and females, revealing a statistically significant difference (χ^2=13.14, p=0.041).

Further analysis of MACE subtypes revealed additional insights. Cerebrovascular disorders accounted for 5.8% of the cohort, with a slightly higher prevalence in males (7.2%) compared to females (4.3%). Myocardial infarction, the most frequent MACE subtype, was observed in 8.2% of participants, occurring in 6.8% of females and 9.6% of males. Pulmonary embolism was less common, affecting 2.4% of individuals, with a higher occurrence in males (3.0%) compared to females (1.9%). The total count of CV mortality was 0.9% (3 patients). The distributions of these subtypes are summarized in Fig. 2. Although there were observable trends in the distribution of MACE subtypes, the chi-square test showed no statistically significant difference between males and females (χ^2=2.23, p=0.33).

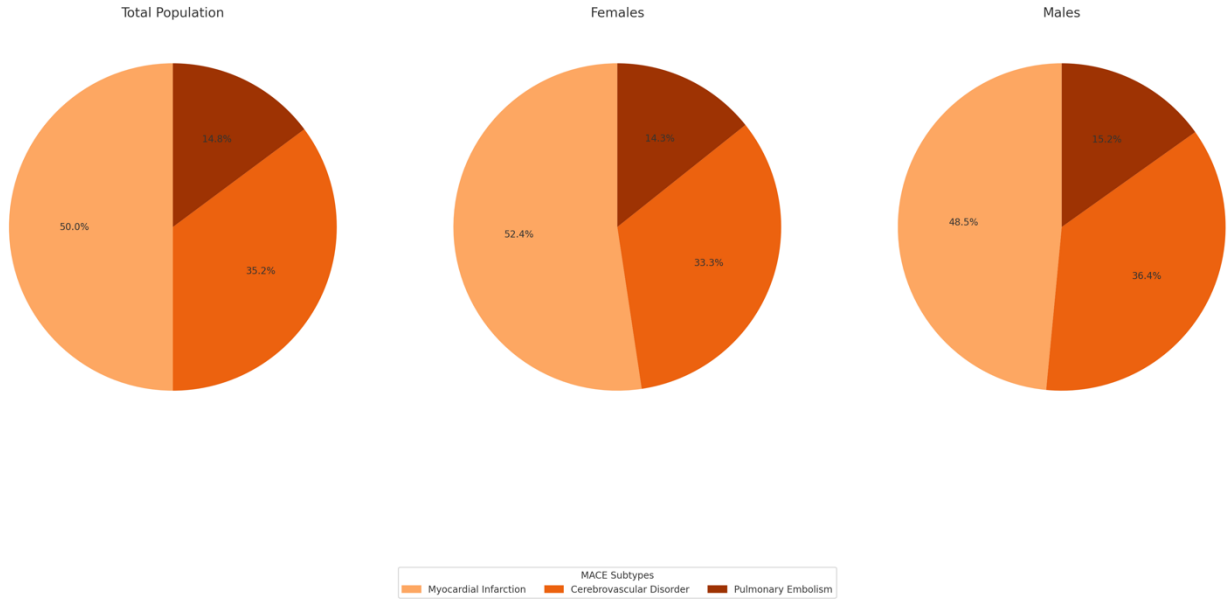

Fig. 2. The characteristics of MACE subtypes in population after COVID-19

To further explore the impact of demographic factors on CV complications, a logistic regression analysis was conducted. The results demonstrated that age and male sex were significant predictors of CV complications. Specifically, each additional year of age increased the odds of CV complications by 4% (OR = 1.04, 95% CI: 1.02–1.07, p = 0.002). Similarly, males were 1.95 times more likely to experience CV complications compared to

females (OR = 1.95, 95% CI: 1.20–3.17, p = 0.007). These findings highlight the influence of both age and sex on the likelihood of developing CV complications in this cohort.

Laboratory investigations revealed several biomarkers with tendencies to differ between participants with and without CV outcomes. Among these, C-reactive protein (CRP) levels were higher in participants with CV outcomes (38.28 ± 1.99 mg/L) compared to those without (35.11 ± 1.12 mg/L), but this difference was not statistically significant enough (p = 0.0661). In contrast, neutrophil-to-lymphocyte ratio (NLR) and D-dimer levels demonstrated significant elevations in participants with CV outcomes. NLR was markedly higher in the affected group (4.78 ± 0.04) compared to those without CV outcomes (3.99 ± 0.04, p < 0.001), while D-dimer levels were nearly 1 mg/L higher in participants with CV outcomes (2.90 ± 0.11 mg/L vs. 1.89 ± 0.07 mg/L, p < 0.001).

Logistic regression further examined the predictive power of these markers. Unfortunately, CRP did not significantly affect the likelihood of CV outcomes (OR = 1.00, 95% CI: 0.98–1.02, p = 0.991). However, NLR strongly influenced CV outcomes, with an odds ratio of 18.18 (95% CI: 9.24–35.80, p < 0.001). Similarly, D-dimer levels significantly increased the risk of CV outcomes (OR = 3.51, 95% CI: 2.33–5.29, p < 0.001).

While the primary focus of this study was on cardiovascular outcomes, an interesting observation emerged regarding diabetes status within the cohort. Among participants without CV complications, 6.4% had first-time detected diabetes, 14.2% had known diabetes, and 79.3% had no diabetes. In contrast, participants with CV complications exhibited a higher prevalence of known diabetes (21.4%) and a similar proportion of first-time detected diabetes (6.8%), with most patients having no diabetes (71.8%). However, the comparison of diabetes status between groups with and without CV outcomes using a chi-squared test revealed that there is no statistically significant difference in the distribution of diabetes status between groups (p=0.2682).

Still, these findings underscore the prevalence of undiagnosed diabetes, with a significant proportion of participants presenting with first-time detected diabetes during hospitalization or the investigation period. Logistic regression analysis showed that the diabetes had an odds ratio of 1.63 (95% CI: 0.88–3.00, p = 0.12). While not statistically significant, the higher prevalence of diabetes among participants with CV complications highlights the need for increased attention to metabolic conditions in the context of post-COVID-19 recovery. These observations suggest that routine diabetes screening during hospitalization could uncover previously undiagnosed cases, potentially informing better clinical management.

The next step of our study was to check the predictive ability of demographic characteristics and biomarkers for CV complications and MACE to understand which factors most strongly influence outcomes. The ROC analysis was conducted for different data both as individual and as a combined factors. Among individual markers, the neutrophil-to-lymphocyte ratio (NLR) consistently emerged as the most reliable predictor, achieving an AUC of 0.86 for CV complications, reflecting its strong association with systemic inflammation and its impact on cardiovascular health. C-reactive protein (CRP) and D-Dimer also demonstrated notable tendencies, with AUC values of 0.54 and 0.74, respectively, suggesting that inflammation and coagulation processes are important contributors to these outcomes. Age, male sex, and diabetes status, while significant factors, had limited predictive power when considered in isolation, highlighting their importance as context-dependent rather than standalone predictors. The integration of multiple predictors revealed much stronger associations. Models combining biomarkers such as CRP, D-Dimer, and NLR showed very high predictive value for both CV complications (AUC = 0.92) and MACE (AUC = 0.76), indicating that these biological processes collectively provide a clearer picture of risk. Adding diabetes status to these models further improved their performance, increasing the AUC to 0.93 for CV complications and 0.78 for MACE, underscoring the incremental value of combining clinical characteristics with biomarker data. The graphical representation of conducted POC analysis in shown in Figures 3-6.

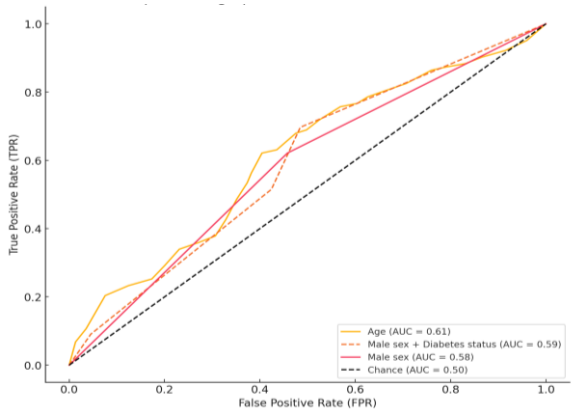

Fig. 3. ROC analysis for individual and combined markers (age and sex) predicting CV outcomes in patients during 12 months after COVID-19

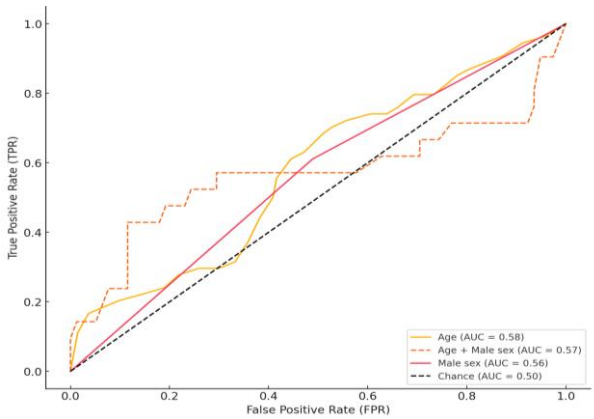

Fig. 4. ROC analysis for individual and combined markers (age and sex) predicting MACE in patients during 12 months after COVID-19

These findings underscore the multifactorial nature of cardiovascular outcomes and MACE risk. Single predictors, while informative, are limited in capturing the

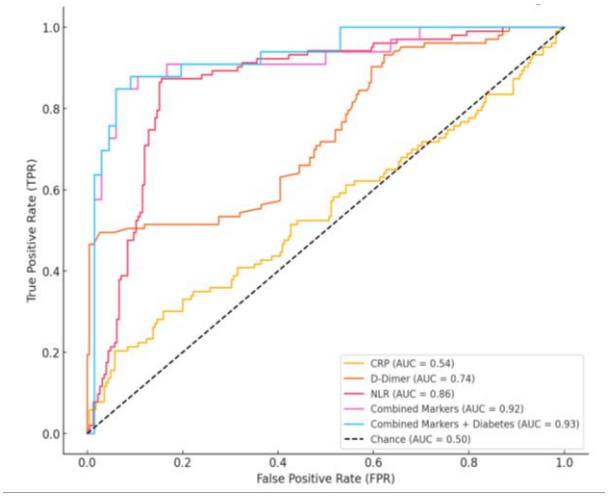

Fig. 5. ROC analysis for individual and combined clinical markers predicting CV outcomes in patients during 12 months after COVID-19

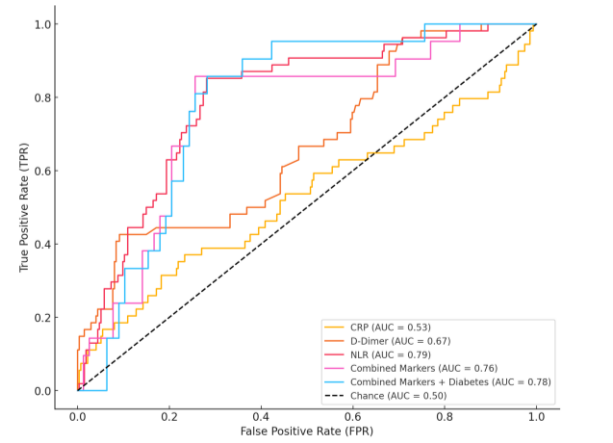

Fig. 6. ROC analysis for individual and combined clinical markers predicting MACE in patients during 12 months after COVID-19

complexity of these conditions. The combination of demographic factors, such as age, sex, and diabetes, with biomarkers offers significantly enhanced predictive performance. This integrated approach is essential for accurate risk stratification and could inform targeted prevention and intervention strategies in clinical practice.

Our study provides a detailed evaluation of long-term cardiovascular (CV) outcomes in COVID-19 survivors. Over the 12-month follow-up period, our findings indicate a significant prevalence of CV complications, including arrhythmias (5.2%), myocardial infarction (8.2%), cerebrovascular disorders (5.8%) and other. These rates highlight the burden of post-COVID-19 sequelae and allow for comparisons with other studies.

For example, the incidence of arrhythmias in our study (5.2%) aligns with findings by Lim et al., who reported similar rates ranging from 4.0% to 5.0% across cohorts [6]. Myocardial infarction rates in our cohort (8.2%) were slightly higher than those documented by Yang et al. (7.1%), potentially due to differences in follow-up duration or population demographics [7]. Similarly, our observed rate of cerebrovascular complications (5.8%) corresponds with Tobler et al., who reported rates of 5.5%, underscoring the systemic nature of COVID-19's impact on the cardiovascular system [8].

Major adverse cardiovascular events (MACE) accounted for 16.5% of the cohort, which is consistent with findings by Lim et al., where a 15.7% increased risk of MACE was observed over a median follow-up of 300 days [6]. These comparable rates across studies strengthen the evidence for the long-term vascular and myocardial consequences of COVID-19 infection.

Myocarditis, though less frequent in our study (2.4%), remains an important post-COVID-19 complication. In contrast, Tobler et al. documented myocarditis in 3.1% of their population, suggesting slight variability across cohorts but consistent recognition of this condition as part of the post-infectious spectrum [8]. These findings emphasize the multifactorial and diverse nature of cardiovascular sequelae in COVID-19 survivors.

Interestingly, we observed a low rate of cardiovascular mortality during the follow-up period. This aligns with findings from other studies that reported cardiovascular death rates between COVID-19 survivors below 1-2% [6, 8]. This may reflect advancements in acute care and post-acute COVID-19 management, as well as the exclusion criteria, which omitted patients with severe comorbidities.

Our study's ability to compare cardiovascular outcome structures across multiple studies highlights the systemic impact of COVID-19 on cardiovascular health. The similarities in findings across diverse populations and research designs strengthen the generalizability of these results and provide valuable insights into the patterns and risks associated with post-COVID-19 cardiovascular complications.

So, the consistent observation of cardiovascular complications, such as MACE and myocarditis, across multiple studies underscores the critical need for long-term cardiovascular surveillance in COVID-19 survivors. Integrating cardiovascular assessment into routine post-COVID care can provide an opportunity for early intervention and targeted management. This approach not only addresses the immediate cardiovascular risks but also contributes to a broader understanding of the long-term sequelae of COVID-19, ultimately improving outcomes and guiding future research efforts.

Biomarkers have also emerged as significant tools for assessing long-term outcomes in COVID-19 survivors. Lehmann et al. identified persistent elevation of D-dimer levels in 15% of patients approximately three months post-recovery. These patients had more severe initial infections and continued to present with respiratory issues, suggesting the prognostic importance of D-dimer in prolonged health risks [9]. Biamonte et al. highlighted the predictive value of combined lymphocyte/monocyte counts, D-dimer, and iron status for disease progression and outcomes in a long-term care facility. Elevated CRP and NLR levels were also associated with severe disease outcomes, underscoring their utility in long-term prognosis assessment [10].

In addition to these findings, numerous studies, including those by Wang et al. and Ye et al., have demonstrated the importance of biomarkers such as D-dimer, CRP, and NLR as prognostic markers for in-hospital prognosis and short-term outcomes [11, 12].

Wang et al. emphasized the predictive value of laboratory indicators, including CRP and NLR, in determining disease progression and mortality during hospitalization [11]. Similarly, Ye et al. identified dynamic changes in D-dimer and NLR as critical indicators of prognosis, focusing on their association with short-term outcomes [12]. While these studies primarily assessed short-term risks, our findings extend the prognostic relevance of these markers to long-term cardiovascular outcomes, highlighting their broader clinical utility.

The pathophysiological mechanisms underlying the prognostic value of these markers in COVID-19-related complications further underscore their importance. Elevated D-dimer reflects a hypercoagulable state characterized by excessive fibrinolysis and thrombus formation, driven by systemic inflammation and endothelial dysfunction. This prothrombotic environment contributes to the increased risk of venous thromboembolism, arterial thrombosis, and myocardial injury [13]. Similarly, elevated CRP, an acute-phase reactant, signals significant systemic inflammation, which exacerbates endothelial damage and promotes thrombus formation. This interplay between inflammation and coagulation heightens the risk of thrombotic events and cardiac injury [14].

The neutrophil-to-lymphocyte ratio (NLR), indicative of immune dysregulation, provides further insights into disease progression. Increased neutrophil counts facilitate the release of neutrophil extracellular traps (NETs), which amplify thrombosis by activating platelets and coagulation pathways. Concurrent lymphopenia impairs immune regulation, exacerbating the inflammatory response and associated thrombotic risks [15]. Together, these mechanisms illustrate the intricate relationship between inflammation, immune dysfunction, and coagulation in COVID-19, further emphasizing the need for targeted management strategies.

In conclusion, the consistent observation of cardiovascular complications, such as MACE and myocarditis, across multiple studies underscores the critical need for long-term cardiovascular surveillance in COVID-19 survivors. Integrating cardiovascular assessment into routine post-COVID care is essential to facilitate early detection and targeted management strategies. This approach addresses immediate cardiovascular risks, fosters a deeper understanding of the chronic sequelae of COVID-19, and highlights the interplay of inflammation, thrombosis, and immune dysregulation as key drivers of adverse outcomes. By emphasizing these interconnected pathways, this study lays a foundation for future research to optimize therapeutic strategies and improve long-term outcomes in this vulnerable population.

Conclusions

1. This study comprehensively evaluated long-term cardiovascular outcomes in COVID-19 survivors, revealing a substantial prevalence of MACE, arrhythmias, and myocardial infarction, which underscores the significant burden of post-COVID cardiovascular sequelae.

2. Elevated neutrophil-to-lymphocyte ratio (NLR) and D-dimer levels were identified as key predictors of adverse outcomes, highlighting the central role of systemic inflammation and coagulation in the pathogenesis of long-term cardiovascular complications.

3. Integration of these biomarkers with demographic and clinical characteristics into predictive models enhances the accuracy of identifying high-risk patients and supports personalized management approaches to improve long-term outcomes.

4. The growing burden of cardiovascular complications necessitates comprehensive post-acute care pathways, including routine cardiovascular screening, early risk detection, and coordinated multidisciplinary management to reduce morbidity and mortality.

5. Long-term cardiovascular surveillance, implementation of predictive frameworks, and strengthened public health strategies are essential to mitigate post-COVID risks, improve patient outcomes, and enhance healthcare system resilience.

List of references

1. Sechi LA, Colussi G, Bulfone L, Brosolo G, Da Porto A, Peghin M, et al. Short-term cardiac outcome in survivors of COVID-19: a systematic study after hospital discharge. Clin Res Cardiol. 2021;110(7):1063-72. doi: 10.1007/s00392-020-01800-z

2. Umbrajkar S, Stankowski RV, Rezkalla S, Kloner RA. Cardiovascular Health and Disease in the Context of COVID-19. Cardiol Res. 2021;12(2):67-79. doi: 10.14740/cr1199

3. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-90. doi: 10.1038/s41591-022-01689-3

4. Rahmati M, Udeh R, Kang J, Dolja-Gore X, McEvoy M, Kazemi A, et al. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of Symptoms 3 Years Post-SARS-CoV-2 Infection. J Med Virol [Internet]. 2025[cited 2025 Oct 19];97(6):e70429. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12143191/pdf/JMV-97-e70429.pdf doi: 10.1002/jmv.70429

5. Bandopadhyay A, Singh AK, Chaubey G. COVID-19: The Cause of the Manifested Cardiovascular Complications During the Pandemic. Front Cardiovasc Med [Internet]. 2021[cited 2025 Oct 19];8:744482. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8581218/pdf/fcvm-08-744482.pdf doi: https://doi.org/10.3389/fcvm.2021.744482

6. Lim JT, Liang En W, Tay AT, Pang D, Chiew CJ, Ong B, et al. Long-term Cardiovascular, Cerebrovascular, and Other Thrombotic Complications in COVID-19 Survivors: A Retrospective Cohort Study. Clin Infect Dis. 2024;78(1):70-9. doi: 10.1093/cid/ciad469

7. Yang Q, Chang A, Tong X, Jackson SL, Merritt RK. Long-term cardiovascular disease outcomes in non-hospitalized medicare beneficiaries diagnosed with COVID-19: Population-based matched cohort study. PLoS One [Internet]. 2024[cited 2025 Oct 15];19(5):e0302593. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11093379/pdf/pone.0302593.pdf doi: 10.1371/journal.pone.0302593

8. Tobler DL, Pruzansky AJ, Naderi S, Ambrosy AP, Slade JJ. Long-Term Cardiovascular Effects of COVID-19: Emerging Data Relevant to the Cardiovascular Clinician. Curr Atheroscler Rep. 2022;24(7):563-70. doi: 10.1007/s11883-022-01032-8

9. Lehmann A, Prosch H, Zehetmayer S, Gysan MR, Bernitzky D, Vonbank K, et al. Impact of persistent D-dimer elevation following recovery from COVID-19. PLoS One [Internet]. 2021[cited 2025 Oct 15];16(10):e0258351. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8553152/pdf/pone.0258351.pdf doi: 10.1371/journal.pone.0258351

10. Biamonte F, Botta C, Mazzitelli M, Rotundo S, Trecarichi EM, Foti D, et al. Combined lymphocyte/monocyte count, D-dimer and iron status predict COVID-19 course and outcome in a long-term care facility. J Transl Med [Internet]. 2021[cited 2025 Oct 19];19(1):79. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7887565/pdf/12967_2021_Article_2744.pdf doi: 10.1186/s12967-021-02744-2

11. Wang Q, Cheng J, Shang J, Wang Y, Wan J, Yan YQ, et al. Clinical value of laboratory indicators for predicting disease progression and death in patients with COVID-19: a retrospective cohort study. BMJ Open [Internet]. 2021[cited 2025 Oct 19];11(10):e043790. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8488281/pdf/bmjopen-2020-043790.pdf doi: 10.1136/bmjopen-2020-043790

12. Ye W, Chen G, Li X, Lan X, Ji C, Hou M, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. Respir Res [Internet]. 2020[cited 2025 Oct 15];21(1):169. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7332531/pdf/12931_2020_Article_1428.pdf doi: 10.1186/s12931-020-01428-7

13. Gerber GF, Chaturvedi S. How to recognize and manage COVID-19-associated coagulopathy. Hematology Am Soc Hematol Educ Program. 2021;2021(1):614-20. doi: 10.1182/hematology.2021000297

14. Gorog DA, Storey RF, Gurbel PA, Tantry US, Berger JS, Chan MY, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat Rev Cardiol. 2022;19(7):475-95. doi: 10.1038/s41569-021-00665-7

15. Li J, Zhang K, Zhang Y, Gu Z, Huang C. Neutrophils in COVID-19: recent insights and advances. Virol J [Internet]. 2023[cited 2025 Oct 15];20(1):169. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10398943/pdf/12985_2023_Article_2116.pdf doi: 10.1186/s12985-023-02116-w

References

1. Sechi LA, Colussi G, Bulfone L, Brosolo G, Da Porto A, Peghin M, et al. Short-term cardiac outcome in survivors of COVID-19: a systematic study after hospital discharge. Clin Res Cardiol. 2021;110(7):1063-72. doi: 10.1007/s00392-020-01800-z

2. Umbrajkar S, Stankowski RV, Rezkalla S, Kloner RA. Cardiovascular Health and Disease in the Context of COVID-19. Cardiol Res. 2021;12(2):67-79. doi: 10.14740/cr1199

3. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28(3):583-90. doi: 10.1038/s41591-022-01689-3

4. Rahmati M, Udeh R, Kang J, Dolja-Gore X, McEvoy M, Kazemi A, et al. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of Symptoms 3 Years Post-SARS-CoV-2 Infection. J Med Virol [Internet]. 2025[cited 2025 Oct 19];97(6):e70429. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC12143191/pdf/JMV-97-e70429.pdf doi: 10.1002/jmv.70429

5. Bandopadhyay A, Singh AK, Chaubey G. COVID-19: The Cause of the Manifested Cardiovascular Complications During the Pandemic. Front Cardiovasc Med [Internet]. 2021[cited 2025 Oct 19];8:744482. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8581218/pdf/fcvm-08-744482.pdf doi: https://doi.org/10.3389/fcvm.2021.744482

6. Lim JT, Liang En W, Tay AT, Pang D, Chiew CJ, Ong B, et al. Long-term Cardiovascular, Cerebrovascular, and Other Thrombotic Complications in COVID-19 Survivors: A Retrospective Cohort Study. Clin Infect Dis. 2024;78(1):70-9. doi: 10.1093/cid/ciad469

7. Yang Q, Chang A, Tong X, Jackson SL, Merritt RK. Long-term cardiovascular disease outcomes in non-hospitalized medicare beneficiaries diagnosed with COVID-19: Population-based matched cohort study. PLoS One [Internet]. 2024[cited 2025 Oct 15];19(5):e0302593. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11093379/pdf/pone.0302593.pdf doi: 10.1371/journal.pone.0302593

8. Tobler DL, Pruzansky AJ, Naderi S, Ambrosy AP, Slade JJ. Long-Term Cardiovascular Effects of COVID-19: Emerging Data Relevant to the Cardiovascular Clinician. Curr Atheroscler Rep. 2022;24(7):563-70. doi: 10.1007/s11883-022-01032-8

9. Lehmann A, Prosch H, Zehetmayer S, Gysan MR, Bernitzky D, Vonbank K, et al. Impact of persistent D-dimer elevation following recovery from COVID-19. PLoS One [Internet]. 2021[cited 2025 Oct 15];16(10):e0258351. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8553152/pdf/pone.0258351.pdf doi: 10.1371/journal.pone.0258351

10. Biamonte F, Botta C, Mazzitelli M, Rotundo S, Trecarichi EM, Foti D, et al. Combined lymphocyte/monocyte count, D-dimer and iron status predict COVID-19 course and outcome in a long-term care facility. J Transl Med [Internet]. 2021[cited 2025 Oct 19];19(1):79. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7887565/pdf/12967_2021_Article_2744.pdf doi: 10.1186/s12967-021-02744-2

11. Wang Q, Cheng J, Shang J, Wang Y, Wan J, Yan YQ, et al. Clinical value of laboratory indicators for predicting disease progression and death in patients with COVID-19: a retrospective cohort study. BMJ Open [Internet]. 2021[cited 2025 Oct 19];11(10):e043790. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC8488281/pdf/bmjopen-2020-043790.pdf doi: 10.1136/bmjopen-2020-043790

12. Ye W, Chen G, Li X, Lan X, Ji C, Hou M, et al. Dynamic changes of D-dimer and neutrophil-lymphocyte count ratio as prognostic biomarkers in COVID-19. Respir Res [Internet]. 2020[cited 2025 Oct 15];21(1):169. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7332531/pdf/12931_2020_Article_1428.pdf doi: 10.1186/s12931-020-01428-7

13. Gerber GF, Chaturvedi S. How to recognize and manage COVID-19-associated coagulopathy. Hematology Am Soc Hematol Educ Program. 2021;2021(1):614-20. doi: 10.1182/hematology.2021000297

14. Gorog DA, Storey RF, Gurbel PA, Tantry US, Berger JS, Chan MY, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat Rev Cardiol. 2022;19(7):475-95. doi: 10.1038/s41569-021-00665-7

15. Li J, Zhang K, Zhang Y, Gu Z, Huang C. Neutrophils in COVID-19: recent insights and advances. Virol J [Internet]. 2023[cited 2025 Oct 15];20(1):169. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10398943/pdf/12985_2023_Article_2116.pdf doi: 10.1186/s12985-023-02116-w

Information about the authors:

Hovornyan A.V. – PhD student of the Department of Propaedeutics of Internal Diseases of Bukovinian State Medical University, Chernivtsi, Ukraine.

E-mail: anastasiia.hv@bsmu.edu.ua

ORCID ID: https://orcid.org/0000-0003-1046-0038

Ilashchuk T.O. – Doctor of Medical Sciences, Professor, Head of the Department of Propaedeutics of Internal Diseases of Bukovinian State Medical University, Chernivtsi, Ukraine.

E-mail: ilashchuk.tetiana@bsmu.edu.ua

ORCID ID: https://orcid.org/0000-0002-0094-8315

Відомості про авторів:
Говорнян А.В. – аспірант кафедри пропедевтики внутрішніх хвороб Буковинського державного медичного університету, м. Чернівці, Україна.
E-mail: anastasiia.hv@bsmu.edu.ua
ORCID ID: https://orcid.org/0000-0003-1046-0038
Ілащук Т.О. – доктор медичних наук, професор, завідувач кафедри пропедевтики внутрішніх хвороб Буковинського державного медичного університету, м. Чернівці, Україна.
E-mail: ilashchuk.tetiana@bsmu.edu.ua
ORCID ID: https://orcid.org/0000-0002-0094-8315

Дата першого надходження рукопису до видання: 25.07.2025
Дата прийнятого до друку рукопису після рецензування: 13.08.2025
Дата публікації: 30.09.2025