ORIGINAL ARTICLE

DOI: 10.4274/e-cvsi.2026.2026-5-2
Cardiovasc Surg Int 2026;13(1):101-110

CARDIOVASCULAR SURGERY AND INTERVENTIONS

Long COVID meets the pump: Identifying who declines after cardiopulmonary bypass

Lütfi Çağatay Onar

Clinic of Cardiovascular Surgery, Dr. İsmail Fehmi Cumalioğlu City Hospital, Tekirdağ, Türkiye

Received: May 08, 2026 **Accepted:** June 09, 2026 **Publication Date:** June 12, 2026

ABSTRACT

Objectives: Long coronavirus (COVID) is increasingly encountered in patients undergoing major cardiac surgery. Cardiopulmonary bypass (CPB) induces systemic inflammation that may overlap with proposed mechanisms of Long COVID; however, its contribution to postoperative symptom progression remains unclear. This study evaluated the prevalence of long COVID and predictors of postoperative symptom worsening in patients undergoing coronary artery bypass surgery.

Patients and methods: This retrospective analysis used prospectively collected perioperative symptom surveillance data from 1,421 adults undergoing CPB-assisted coronary artery bypass grafting, with or without concomitant valve surgery (November 2020-September 2025). Only patients with a complete 3-month follow-up were included. Symptoms were assessed preoperatively and at 3 months using a structured questionnaire and scoring system.

Results: Long COVID symptoms were present in 5.6% of patients. Affected individuals were more often ≥65 years, female, and had poor glycemic control, severe obesity, repeated COVID-19 infections, sleep disturbances, and neuropsychiatric or immunologic disorders. The factor V Leiden mutation was more frequent. Symptom worsening was independently associated with HbA1c >9%, multivessel coronary artery disease, severe obesity, and neuropsychiatric or immunologic comorbidities. CPB exposure was not independently associated with symptom progression.

Conclusion: CPB was not associated with increased progression of postoperative symptoms. Findings suggest that symptom worsening is primarily related to underlying metabolic and neuropsychiatric vulnerability, supporting the importance of perioperative risk stratification.

Keywords: Long COVID, cardiopulmonary bypass, coronary artery bypass grafting, postoperative complications, risk factors.

Long coronavirus (COVID) syndrome, also referred to as post-acute coronavirus disease-2019 (COVID-19) condition, is increasingly recognized as a heterogeneous multisystem disorder characterized by persistent fatigue, dyspnea, neurocognitive impairment, dysautonomia, sleep disturbance, and affective symptoms following severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.[1-3]

Persistent symptoms have been documented across a wide spectrum of clinical severity and may substantially affect functional recovery and quality of life.[4,5] Although initially described in ambulatory populations, subsequent studies have demonstrated that symptom persistence is also common after hospitalization, with measurable physical, cognitive, and psychological impairment extending beyond the acute phase of illness.[6,7] Reduced physical performance and impaired functional capacity at hospital discharge further suggest sustained physiologic vulnerability in affected patients.[8]

The pathophysiology of long COVID appears multifactorial and includes persistent immune activation, endothelial dysfunction, autonomic imbalance, and thromboinflammatory signaling.[9,10] Endothelial injury and microvascular inflammation may contribute to ongoing multisystem symptoms and prolonged recovery.[10] Cardiovascular involvement following SARS-CoV-2 infection has also been increasingly recognized, including myocardial inflammation and long-term cardiovascular sequelae.[11,12] These findings suggest that patients with long COVID may present with underlying physiologic vulnerability that could influence perioperative outcomes.

Cardiac surgery performed with cardiopulmonary bypass (CPB) represents a particularly relevant physiologic setting in which postoperative symptom evolution may differ from that observed in non-surgical populations. CPB induces a systemic inflammatory response characterized by endothelial activation, cytokine release, oxidative stress,

Address for Correspondence: Lütfi Çağatay Onar, MD, Clinic of Cardiovascular Surgery, Dr. İsmail Fehmi Cumalioğlu City Hospital, Tekirdağ, Türkiye
E-mail: lutficagatay.onar@saglik.gov.tr **ORCID ID:** orcid.org/0000-0002-7767-9029
Cite this article as: Onar LÇ. Long COVID meets the pump: identifying who declines after cardiopulmonary bypass. Cardiovasc Surg Int. 2026;13(1):101-110

and microvascular dysfunction.[13] In addition, perioperative alterations in cerebral perfusion, microembolic exposure, and neurohumoral stress may contribute to postoperative neurocognitive dysfunction.[14] These mechanisms overlap with domains commonly affected in long COVID, including cognitive impairment and autonomic dysregulation.

Beyond systemic inflammatory activation, CPB is associated with alterations in microcirculatory flow, endothelial permeability, and coagulation pathways, which may influence postoperative recovery. These effects may be particularly relevant in patients with pre-existing endothelial dysfunction or persistent immune activation, both of which have been implicated in long COVID.

In this context, patients undergoing coronary artery bypass grafting (CABG) with CPB represent a population that substantially overlaps with established long COVID risk groups. Advanced age, diabetes mellitus, obesity, and cardiometabolic disease have all been associated with increased persistence of post-COVID-19 symptom burden.[4,5,11] These comorbidities are highly prevalent in contemporary cardiac surgical cohorts.[15] Emerging evidence also suggests that autoimmune and inflammatory mechanisms may contribute to symptom persistence in susceptible individuals.[9]

Despite these considerations, data describing longitudinal symptom evolution in patients with long COVID undergoing cardiac surgery remain limited. Most available studies have focused on early postoperative morbidity rather than on the structured assessment of symptom trajectories beyond hospital discharge.[16] This represents an important knowledge gap, particularly as the number of patients with prior SARS-CoV-2 infection undergoing cardiac surgery continues to increase.

To address this knowledge gap, we performed a retrospective analysis of prospectively collected institutional perioperative symptom surveillance data from a large cohort of patients undergoing CABG with CPB, with or without concomitant valve surgery. The objectives were to determine the prevalence of long COVID, characterize longitudinal symptom trajectories, and identify predictors of clinically meaningful postoperative symptom worsening.

PATIENTS AND METHODS

Study Design and Reporting Standards

This study is a retrospective analysis of prospectively collected data from an institutional perioperative symptom surveillance program. The surveillance program was introduced in November 2020 to clinically monitor persistent post-infectious and vaccination-related symptoms in patients undergoing cardiac surgery requiring CPB. Subsequently, the scientific relevance of the accumulated dataset was recognized, and a structured research protocol was developed. Ethical approval was obtained from the Institutional Ethics Committee of Dr. İsmail Fehmi Cumalioğlu City Hospital (approval number: AN-261203-16, date: 12.03.2026). The present investigation therefore combines prospective data acquisition with a retrospective, hypothesis-driven analysis.

The study was designed to evaluate perioperative symptom trajectories in patients with prior SARS-CoV-2 infection and to determine predictors of postoperative symptom worsening. The study adhered to the strengthening the reporting of observational studies in epidemiology recommendations for observational cohort studies.[17] The study was conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent was waived by the ethics committee because the study was observational. No prespecified sample size calculation was performed because all consecutive eligible patients within the study period were included

Study Population

Between November 1, 2020, and September 30, 2025, consecutive adult patients undergoing CABG performed with CPB, with or without concomitant valve procedures, were included. Patients undergoing emergent surgery were excluded because acute perioperative instability may confound longitudinal symptom assessment. Off-pump procedures were excluded to isolate the physiologic effects attributable to CPB. Additional exclusion criteria included isolated valve procedures, isolated aortic surgery, preoperative mechanical circulatory support, stroke within 90 days before surgery, incomplete symptom assessment, and missing three-month follow-up data.

To ensure complete three-month postoperative follow-up data were available at the time of analysis, patients undergoing surgery after September 30, 2025, were excluded from the final dataset.

Exposure Variables and Operative Management

Standard CPB techniques with moderate systemic hypothermia and conventional perfusion strategies were used. CPB duration was modeled as a continuous exposure variable, and potential non-linearity was assessed using restricted cubic splines.

Recorded intraoperative variables included aortic cross-clamp time, nadir temperature, cardioplegia characteristics, intraoperative hematocrit, degree of hemodilution, transfusion requirements, peak lactate concentration, vasoactive and inotropic support, intraoperative arrhythmias, low cardiac output syndrome, and regional cerebral oxygen saturation measured by near-infrared spectroscopy.

SARS-CoV-2 Exposure Variables

Confirmed SARS-CoV-2 infection was defined as documented polymerase chain reaction or antigen positivity or hospitalization attributable to COVID-19. Infection burden was modeled as an ordinal variable based on the number of infection episodes. Additional variables included COVID-19–related hospitalization, intensive care unit (ICU) admission, mechanical ventilation, vaccination dose count, and the interval between infection and surgery.

Sensitivity analyses were prespecified according to the infection-to-surgery interval (<6 months *vs.* ≥6 months) and restricted to laboratory-confirmed infection.

Baseline Clinical Variables

Baseline demographic, clinical, and laboratory variables were collected prospectively, including cardiometabolic risk factors, neurologic and psychiatric comorbidities, inflammatory biomarkers, and established surgical risk scores.

Long COVID Definition

Long COVID was defined as the persistence of symptoms for at least 12 weeks after confirmed SARS-CoV-2 infection without an alternative explanation, consistent with the World Health

Organization post-COVID-19 condition criteria.[18] Symptom burden was assessed using a structured long COVID questionnaire (LCQ), which was administered preoperatively and again at three months postoperatively. A composite symptom score was calculated, and clinically meaningful worsening was predefined as an increase of at least five points.

Predefined Predictive Risk Phenotype

An a priori metabolic and neuropsychiatric vulnerability phenotype was constructed based on biological plausibility. The phenotype included HbA1c >9%, body mass index ≥36 kg/m², three-vessel coronary artery disease, neurologic, psychiatric, and immunologic disease, and an infection-to-surgery interval <6 months. The cumulative number of phenotype components was modeled as an ordinal variable.

Outcomes

The primary outcome was clinically meaningful worsening of long COVID symptoms at three months. Secondary outcomes included the change in the composite symptom score, domain-specific symptom trajectories, and the interaction between CPB exposure and the predefined vulnerability phenotype.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Group comparisons were performed using parametric or non-parametric tests, as appropriate. Longitudinal symptom evolution was analyzed using mixed-effects models for repeated measures. Multivariable logistic regression was used to identify predictors of symptom worsening. The interaction between CPB duration and the predefined vulnerability phenotype was tested. Multicollinearity was assessed using variance inflation factors. Model discrimination was evaluated using the area under the receiver operating characteristic curve, and calibration was evaluated using the Hosmer-Lemeshow test. Internal validation was performed using bootstrap resampling with 1,000 iterations. When missing data were below 5%, complete-case analysis was used. Statistical significance was defined as two-sided $p<0.05$. All analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Study Population and Long COVID Prevalence

Between November 2020 and September 2025, 1,421 consecutive adult patients who underwent CABG with CPB, with or without concomitant valve procedures, met the inclusion criteria. Prior confirmed SARS-CoV-2 infection was documented in 912 patients (64.2%). At baseline, long COVID symptoms were identified in 80 patients, corresponding to 5.6% of the overall cohort and 8.8% of previously infected individuals. At three months, symptom trajectories improved in 41 patients (51.3%), remained stable in 27 (33.7%), and worsened in 12 (15.0%). The study flow and symptom evolution are illustrated in Figure 1.

Demographic and Vascular Vulnerability Profile

Patients with long COVID differed substantially from those without persistent symptoms in demographic characteristics, cardiometabolic burden, and markers of systemic vascular vulnerability (Table 1).

Patients with long COVID were older, more often female, and had higher body mass index, increased waist-hip ratio, and lower ankle-brachial index values. Reinfection burden and recent infection within six months before surgery were more common, and rates of COVID-19-related hospitalization and ICU admission were higher. Frailty scores and operative risk estimates were also significantly higher in the long COVID group.

Baseline Clinical and Laboratory Characteristics

Baseline clinical characteristics demonstrated clustering of metabolic, neurologic, immunologic, and inflammatory comorbidities among patients with long COVID (Table 2).

Patients with long COVID had a higher prevalence of diabetes mellitus, poor glycemic control (particularly HbA1c >9%), obstructive sleep apnea, and neurologic, psychiatric, and immunologic disorders. Laboratory findings indicated a persistent inflammatory and prothrombotic profile, reflected by elevated CRP, ferritin, fibrinogen, and D-dimer levels, along with lower albumin and hemoglobin concentrations. Symptomatic ≥70% carotid artery stenosis was also more frequent in patients with long COVID.

Operative Characteristics and Early Postoperative Outcomes

Operative characteristics and CPB parameters were comparable between patients with and without postoperative worsening of symptoms (Table 3).

No significant differences were observed in CPB duration, aortic cross-clamp time, intraoperative hematocrit, cardioplegia volume, transfusion

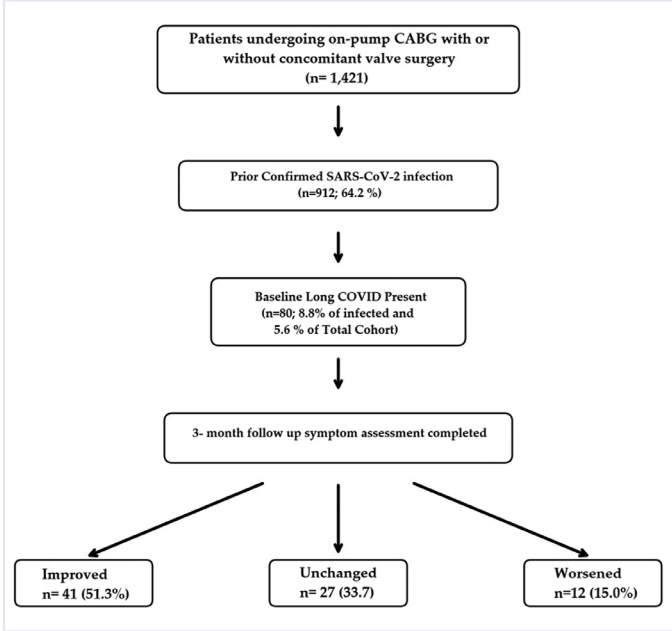

Figure 1. Study flow diagram and postoperative symptom trajectories. Flow of consecutive patients undergoing coronary artery bypass grafting (CABG) performed with cardiopulmonary bypass, with or without concomitant valve procedures. The diagram illustrates prior severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection status, baseline long coronavirus (COVID) prevalence, and the distribution of symptom trajectories at three-month follow-up (improved, unchanged, worsened).

Table 1. Demographic characteristics, cardiometabolic profile, and markers of systemic vascular vulnerability according to long COVID status

Variable	Long COVID (n=80)	No long COVID (n=1.341)	p-value
Age (years)	67.8±8.9	63.4±9.7	<0.001
Female sex	32 (40.0%)	302 (22.5%)	<0.001
BMI (kg/m²)	31.7±4.6	28.9±4.1	<0.001
BMI ≥36 kg/m²	14 (17.5%)	108 (8.1%)	0.004
Waist-hip ratio	0.96±0.08	0.92±0.07	0.002
Ankle-brachial index	0.86±0.11	0.93±0.09	<0.001
Current smoker	21 (26.3%)	412 (30.7%)	0.38
Former smoker	34 (42.5%)	487 (36.3%)	0.27
Educational level ≤8 years	46 (57.5%)	528 (39.4%)	0.002
Sedentary lifestyle	39 (48.7%)	471 (35.1%)	0.01
Confirmed prior SARS-CoV-2 infection	80 (100%)	832 (62.0%)	—
Reinfection count	1.88±0.91	1.36±0.71	<0.001
Last infection <6 months	26 (32.5%)	200 (14.9%)	<0.001
Hospitalized COVID	18 (22.5%)	129 (9.6%)	<0.001
COVID-19 ICU admission	7 (8.8%)	41 (3.1%)	0.008
Mechanical ventilation history	4 (5.0%)	17 (1.3%)	0.01
Vaccination doses	2.3±1.2	2.8±1.1	0.002
NYHA class III-IV	39 (48.7%)	399 (29.7%)	<0.001
LVEF (%)	48.9±9.4	51.8±8.6	0.01
Frailty score	4.6±1.1	3.6±1.2	<0.001
EuroSCORE II (%)	3.92±2.21	2.77±1.89	<0.001
STS mortality risk (%)	2.94±1.71	2.16±1.42	0.001

Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage). BMI: Body mass index; LVEF: Left ventricular ejection fraction; NYHA, New York Heart Association; STS: Society of thoracic surgeons risk score; COVID: Coronavirus; COVID-19: Coronavirus disease-2019; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

requirements, or intraoperative metabolic stress markers. Among early postoperative outcomes, delirium and the need for postoperative rehabilitation were more frequent in the worsening group.

Longitudinal Symptom Burden

A longitudinal mixed-effects analysis demonstrated heterogeneous postoperative symptom trajectories within the long COVID cohort (Table 4).

Greater increases in composite LCQ score were observed in patients with a recent infection (<6 months), severe obesity, poor glycemic control, neurologic or psychiatric disorders, immunologic disorders, and higher frailty scores. Procedural complexity, including concomitant valve surgery, was not associated with symptom progression.

The distribution of changes in composite LCQ scores is illustrated in Figure 2A. The largest increases were observed in patients with recent infection, severe obesity, poor glycemic control, neurologic or psychiatric disease, immunologic disorders, and elevated frailty scores. Subgroup effect sizes are summarized in Figure 2B. The ranked contribution of each vulnerability factor to symptom worsening risk is illustrated in Figure 2C.

Pandemic Variant Era

The distribution of index SARS-CoV-2 infections across pandemic variant periods differed significantly between groups (Table 5).

Patients with long COVID were more frequently infected during earlier pandemic waves (2020-2021), whereas infections during later periods (2024-2025) were less common among these patients. Temporal distribution across variant periods is presented in Table 5.

SARS-CoV-2 Exposure Severity

Measures of cumulative SARS-CoV-2 exposure severity and recency differed significantly between patients with and without long COVID (Table 6).

Patients with persistent symptoms had higher reinfection counts, shorter infection-to-surgery intervals, and higher rates of COVID-19–related hospitalization, ICU admission, and prior mechanical ventilation. The number of vaccine doses was lower in the Long COVID group.

Multivariable Predictors of Postoperative Symptom Worsening

Multivariable logistic regression identified body mass index ≥36 kg/m², HbA1c >9%, three-vessel coronary artery disease, neurologic disease, psychiatric disease, immunologic disease, infection-to-surgery interval <6 months, and frailty score ≥5 as independent predictors of clinically meaningful postoperative symptom worsening (Table 7).

CPB duration showed borderline statistical significance, and no interaction was observed between female sex and HbA1c. A graphical representation of adjusted odds ratios is provided in Figure 2D.

Table 2. Baseline clinical comorbidities, laboratory findings, and SARS-CoV-2 exposure characteristics according to long COVID status

Variable	Long COVID-19 (n=80)	No long COVID-19 (n=1.341)	p-value
Hypertension	64 (80.0%)	964 (71.9%)	0.12
Diabetes mellitus	46 (57.5%)	490 (36.5%)	<0.001
HbA1c (%)	8.9±1.8	7.7±1.5	<0.001
HbA1c >9%	21 (26.3%)	141 (10.5%)	<0.001
COPD	17 (21.3%)	204 (15.2%)	0.14
Obstructive sleep apnea	19 (23.8%)	179 (13.3%)	0.009
Neurologic disease	21 (26.3%)	153 (11.4%)	<0.001
Psychiatric disease	27 (33.8%)	182 (13.6%)	<0.001
Immunologic disease	12 (15.0%)	84 (6.3%)	0.003
Factor V Leiden mutation	8 (10.0%)	50 (3.7%)	0.006
≥70% symptomatic carotid artery stenosis	11 (13.8%)	83 (6.2%)	0.01
Confirmed prior SARS-CoV-2 infection	80 (100%)	832 (62.0%)	—
Reinfection count (ordinal)	1.88±0.91	1.36±0.71	<0.001
Time from last infection to surgery (months)	8.1±4.7	11.4±6.2	<0.001
Last infection <6 months	26 (32.5%)	200 (14.9%)	<0.001
Hospitalized COVID-19 history	18 (22.5%)	129 (9.6%)	<0.001
COVID-19 ICU admission	7 (8.8%)	41 (3.1%)	0.008
Prior mechanical ventilation	4 (5.0%)	17 (1.3%)	0.01
Vaccination doses	2.3±1.2	2.8±1.1	0.002
Variant period 2020-2021	29 (36.3%)	275 (20.5%)	0.002
Variant period 2022-2023	39 (48.7%)	654 (48.8%)	0.98
Variant period 2024-2025	12 (15.0%)	412 (30.7%)	0.004
LVEF (%)	48.9±9.4	51.8±8.6	0.01
LVEF <40%	16 (20.0%)	197 (14.7%)	0.19
NYHA class III-IV	39 (48.7%)	399 (29.7%)	<0.001
Creatinine (mg/dL)	1.32±0.48	1.20±0.41	0.03
eGFR (mL/min/1.73 m²)	61.7±17.9	69.0±18.5	0.002
Hemoglobin (g/dL)	12.1±1.7	13.0±1.8	<0.001
Preoperative anemia	29 (36.3%)	289 (21.6%)	0.002
Albumin (g/dL)	3.6±0.5	3.9±0.4	<0.001
CRP (mg/L)	12.8±6.3	7.2±4.9	<0.001
Ferritin (ng/mL)	364±168	279±141	<0.001
Fibrinogen (mg/dL)	452±121	409±106	0.002
D-dimer (µg/mL)	1.06±0.54	0.76±0.38	<0.001
Frailty score	4.6±1.1	3.6±1.2	<0.001
EuroSCORE II (%)	3.92±2.21	2.77±1.89	<0.001
STS predicted mortality (%)	2.94±1.71	2.16±1.42	0.001

Values are expressed as mean ± standard deviation or number (percentage). CRP: C-reactive protein; eGFR: Estimated glomerular filtration rate; ICU: Intensive care unit; STS: Society of Thoracic Surgeons risk score; LVEF: Left ventricular ejection fraction; NYHA, New York Heart Association; COVID: Coronavirus; COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2; COPD: Chronic obstructive pulmonary disease.

DISCUSSION

In this retrospective analysis of prospectively collected data from a perioperative surveillance program, we observed heterogeneous postoperative trajectories of long COVID symptoms among patients undergoing CABG with CPB. Clinically meaningful worsening occurred primarily in patients with metabolic, neuropsychiatric, and frailty-related vulnerability features, whereas CPB duration showed only a modest association with postoperative symptom burden. These findings suggest that postoperative evolution of long COVID following cardiac surgery is largely determined by host susceptibility rather than by procedural exposure alone.

Long COVID is increasingly recognized as a multisystem condition characterized by persistent immune activation, endothelial dysfunction, autonomic imbalance, and neurocognitive vulnerability.[1-3,9,10] These mechanisms overlap with physiologic responses triggered by CPB, including systemic inflammation, endothelial activation, oxidative stress,

Table 3. Operative characteristics, CPB parameters, and early postoperative outcomes according to postoperative long COVID symptom worsening (any degree of worsening at any timepoint by subjective report, including transient worsening, n=28; clinically meaningful worsening defined as ΔLCQ ≥5 points confirmed by objective assessment at three months, n=12)

Variable	Symptom worsening (n=28)	No worsening (n=52)	p-value
Operative characteristics			
Number of distal anastomoses	3.4±0.9	3.2±1.0	0.31
Concomitant valve procedure	7 (25.0%)	11 (21.2%)	0.68
Total operative time (min)	274±61	261±55	0.29
Cardiopulmonary bypass parameters			
CPB duration (min)	108±34	101±29	0.22
Aortic cross-clamp time (min)	74±22	69±19	0.26
Lowest core temperature (°C)	32.1±1.4	32.4±1.3	0.18
Intraoperative hematocrit (%)	23.8±3.1	24.6±2.8	0.17
Crystalloid cardioplegia volume (mL)	1280±340	1210±310	0.33
Packed RBC transfusion (units)	1.8±1.2	1.5±1.0	0.21
Peak intraoperative lactate (mmol/L)	3.1±1.4	2.7±1.2	0.14
Vasopressor requirement	11/28 (39.3%)	17 (32.7%)	0.53
Inotropic support	9 (32.1%)	14 (26.9%)	0.61
NIRS desaturation episodes	6 (21.4%)	8 (15.4%)	0.48
Early postoperative outcomes			
Delirium	8/28 (28.6%)	6 (11.5%)	0.048
New neurologic deficit/stroke	2 (7.1%)	2 (3.8%)	0.59
New-onset atrial fibrillation	10 (35.7%)	16 (30.8%)	0.64
Prolonged ventilation (>24 h)	7/28 (25.0%)	6 (11.5%)	0.11
Re-intubation	2 (7.1%)	1 (1.9%)	0.26
Acute kidney injury (KDIGO ≥2)	5 (17.9%)	5 (9.6%)	0.28
Deep sternal wound infection	1 (3.6%)	1 (1.9%)	0.66
Reoperation for bleeding	2 (7.1%)	3 (5.8%)	0.81
ICU length of stay (days)	2.9±1.7	2.3±1.2	0.07
Hospital length of stay (days)	8.7±3.4	7.9±2.8	0.21
30-day mortality	1 (3.6%)	1 (1.9%)	0.66
90-day readmission	4 (14.3%)	5 (9.6%)	0.52
Postoperative rehabilitation needs	9 (32.1%)	8 (15.4%)	0.048

Continuous variables are reported as mean ± standard deviation. CPB: Cardiopulmonary bypass; NIRS: Near-infrared spectroscopy; RBC: Red blood cell; ICU: Intensive care unit; COVID: Coronavirus; LCQ: Long COVID questionnaire.

and microvascular perturbation.[13] In addition, neurologic vulnerability after cardiac surgery is influenced by cerebral hypoperfusion, microembolization, and perioperative neuroinflammation.[14] Based on these pathophysiologic parallels, it has been hypothesized that CPB might exacerbate pre-existing long COVID manifestations. However, the present findings do not demonstrate uniform deterioration associated with bypass exposure. Instead, symptom progression appeared to cluster within identifiable high-risk clinical phenotypes, suggesting that CPB may act as a permissive stressor rather than a primary driver of symptom persistence.

The demographic and clinical profile observed in the present cohort is consistent with previous reports describing risk factors for persistent post-COVID-19 symptoms. Older age, female sex, obesity, and diabetes mellitus have been repeatedly associated with prolonged symptom burden in observational studies.[3,4] Similarly, post-hospitalization cohorts have demonstrated persistent functional limitation and reduced exercise tolerance even after resolution of acute infection[6,8] Cardiovascular involvement following SARS-CoV-2 infection, including myocardial inflammation and endothelial dysfunction, may further impair perioperative adaptation in patients undergoing coronary surgery.[11,12] The enrichment of these characteristics among patients with long COVID in the present study supports the concept that persistent symptoms reflect an underlying systemic vulnerability rather than an isolated residual infection.

Metabolic dysregulation emerged as a central determinant of postoperative symptom evolution. Severe obesity and poor glycemic control were independently associated with clinically meaningful worsening. This observation is biologically plausible, as hyperglycemia amplifies endothelial injury, oxidative stress, and inflammatory signaling pathways implicated in long COVID pathophysiology.[3,9,10]

Table 4. Change in composite long COVID symptom score (ΔLCQ) and subgroup analysis of predefined clinical vulnerability features

Subgroup	n	Preoperative LCQ score	Postoperative LCQ score	ΔLCQ score (postop-preop)	Clinically meaningful worsening (%)	Time × subgroup interaction p-value
Entire long COVID-19 cohort	80	15.8±4.2	17.6±4.8	+1.8±2.9	28 (35.0%)	—
Confirmed PCR/antigen-positive infection only	64	15.9±4.3	17.8±4.9	+1.9±3.0	23 (35.9%)	0.82
Time since last infection <6 months	26	15.2±4.1	18.3±5.2	+3.1±3.4	14 (53.8%)	0.004
Time since last infection ≥6 months	54	16.1±4.3	17.3±4.5	+1.2±2.5	14 (25.9%)	Reference
Isolated CABG	62	15.7±4.1	17.3±4.6	+1.6±2.7	20 (32.3%)	0.41
CABG + valve procedure	18	16.1±4.5	18.5±5.1	+2.4±3.2	8 (44.4%)	Reference
Diabetes mellitus	46	15.5±4.0	18.1±4.9	+2.6±3.1	20 (43.5%)	0.01
No diabetes	34	16.2±4.4	17.1±4.3	+0.9±2.2	8 (23.5%)	Reference
Female sex	32	15.3±4.1	18.0±5.0	+2.7±3.3	15 (46.9%)	0.02
Male sex	48	16.1±4.3	17.2±4.5	+1.1±2.4	13 (27.1%)	Reference
Age ≥65 years	52	15.6±4.2	17.9±4.8	+2.3±3.0	21 (40.4%)	0.03
Age <65 years	28	16.2±4.1	17.1±4.2	+0.9±2.1	7 (25.0%)	Reference
BMI ≥36 kg/m²	14	15.0±4.0	18.4±5.3	+3.4±3.6	9 (64.3%)	<0.001
BMI <36 kg/m²	66	16.0±4.3	17.4±4.5	+1.4±2.5	19 (28.8%)	Reference
HbA1c >9%	21	15.1±4.2	18.7±5.4	+3.6±3.5	12 (57.1%)	0.002
HbA1c ≤9%	59	16.0±4.2	17.2±4.4	+1.2±2.3	16 (27.1%)	Reference
Neurologic disease present	21	15.2±4.1	18.3±5.0	+3.1±3.2	12 (57.1%)	0.003
Neurologic disease absent	59	16.0±4.2	17.2±4.5	+1.2±2.4	16 (27.1%)	Reference
Psychiatric disease present	27	15.0±4.0	18.3±5.2	+3.3±3.4	15 (55.6%)	0.002
Psychiatric disease absent	53	16.2±4.2	17.2±4.3	+1.0±2.2	13 (24.5%)	Reference
Immunologic disease present	12	15.1±4.3	18.6±5.6	+3.5±3.7	7 (58.3%)	0.008
Immunologic disease absent	68	15.9±4.2	17.4±4.5	+1.5±2.6	21 (30.9%)	Reference
Frailty score ≥5	34	15.2±4.1	18.2±5.1	+3.0±3.3	18 (52.9%)	0.001
Frailty score <5	46	16.2±4.2	17.2±4.2	+1.0±2.1	10 (21.7%)	Reference

ΔLCQ represents the postoperative score minus the preoperative score. Clinically meaningful worsening was defined as ΔLCQ ≥5. Interaction p-values were derived from mixed-effects repeated-measures models. COVID: Coronavirus; LCQ: Long COVID questionnaire; COVID-19: Coronavirus disease-2019; PCR: Polymerase chain reaction; BMI: Body mass index.

In addition, metabolic disease is a well-established determinant of postoperative recovery after CABG.[15] These findings therefore suggest that metabolic vulnerability may represent a shared mechanistic substrate linking long COVID and adverse postoperative recovery and highlight the importance of perioperative metabolic optimization in this population.

Neuropsychiatric and immunologic comorbidities also showed strong associations with postoperative symptom worsening. Long COVID has been linked to persistent neuroinflammatory activation and dysregulation of central autonomic networks.[3,9] Cardiac surgery introduces additional neurologic stress via fluctuations in cerebral perfusion and activation of inflammatory pathways.[14] The interaction between these factors may explain why symptom deterioration in the present cohort was concentrated among patients with pre-existing neurologic or psychiatric disease. These findings support a vulnerability model in which postoperative symptom progression reflects amplification of pre-existing neuroimmune susceptibility rather than *de novo* injury.

Another important observation was an association between a shorter infection-to-surgery interval and worsening of postoperative symptoms. Patients undergoing surgery within six months of SARS-CoV-2 infection experienced less favorable trajectories, suggesting persistence of physiologic instability beyond the acute phase. Previous perioperative studies have focused primarily on early postoperative complications; however, emerging data in cardiac surgery populations with prior SARS-CoV-2 infection suggest increased vasoactive requirements, thromboembolic risk, and altered postoperative recovery patterns, although longitudinal symptom trajectories remain poorly characterized.[19-21] The present data extend this concept by demonstrating a time-dependent relationship between the recency of infection and postoperative symptom burden in patients undergoing cardiac surgery.

Although CPB duration retained a modest association with symptom worsening, the absence of consistent relationships between other intraoperative variables and postoperative trajectories suggests that procedural exposure alone is insufficient to explain symptom evolution. Instead, CPB appears to interact with host vulnerability factors. From a clinical perspective, this distinction is important. It indicates that the presence of long COVID should not be interpreted as a contraindication to on-pump coronary surgery. Perioperative risk appears to be stratifiable by metabolic control, frailty, neuropsychiatric burden, and recency of infection.

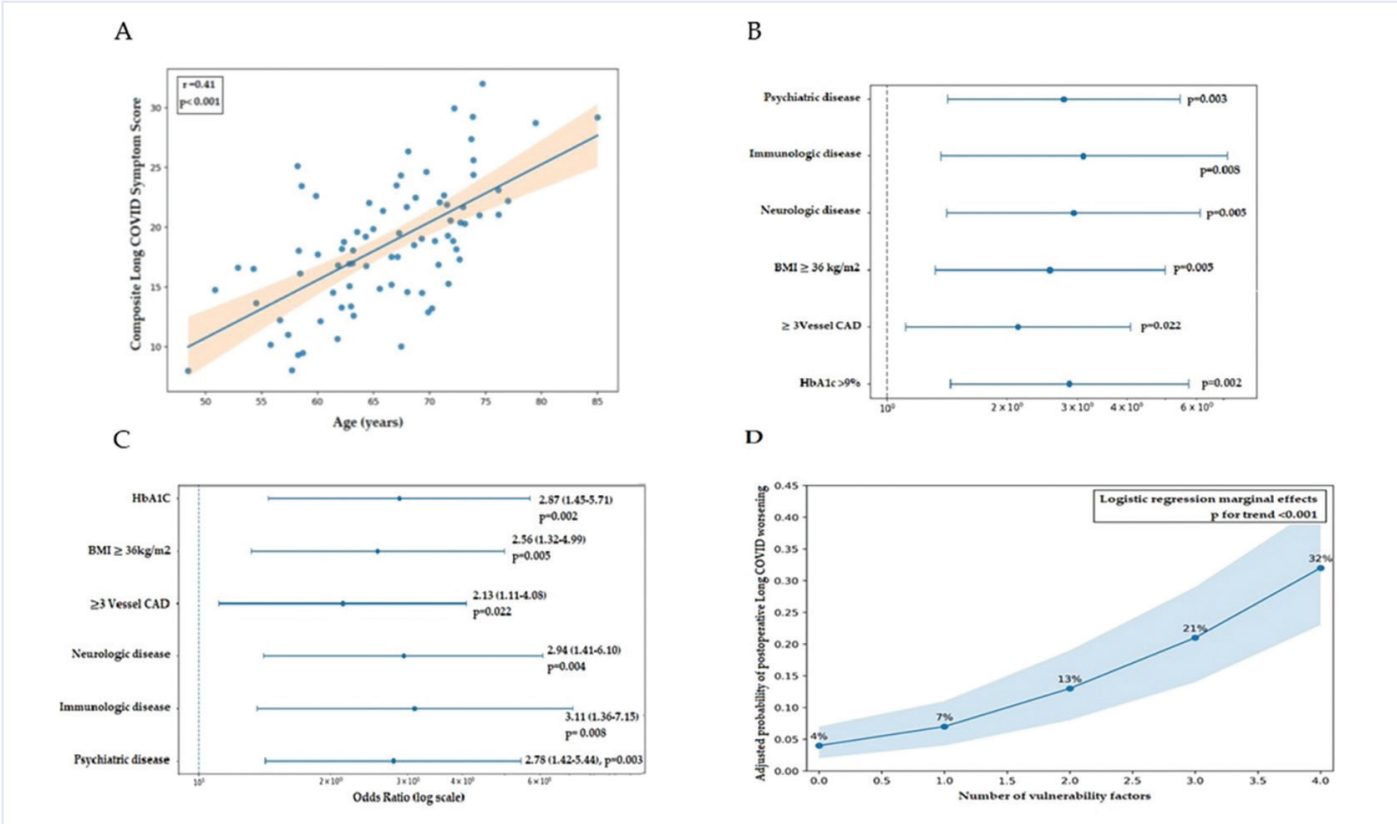

Figure 2. Longitudinal symptom burden and vulnerability subgroup analysis. (A) Distribution of change in composite long coronavirus (COVID) questionnaire (LCQ) scores between preoperative assessment and three-month follow-up. (B) Subgroup forest plot showing the association of predefined vulnerability characteristics with postoperative long COVID symptom worsening, ranked by effect size. (C) Forest plot showing adjusted odds ratios for independent predictors of clinically meaningful postoperative symptom worsening derived from multivariable logistic regression. (D) Adjusted probability of postoperative long COVID worsening according to the number of cumulative vulnerability factors, derived from logistic regression marginal effects analysis.

Table 5. Distribution of index SARS-CoV-2 infection according to pandemic variant period and association with long COVID prevalence

Variant period	Long COVID-19	No long COVID-19	p-value
2020-2021	29 (36.3%)	275 (20.5%)	0.002
2022-2023	39 (48.7%)	654 (48.8%)	0.98
2024-2025	12 (15.0%)	412 (30.7%)	0.004

COVID: Coronavirus; COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

Table 6. Markers of SARS-CoV-2 exposure severity and infection recency in patients with and without long COVID undergoing cardiac surgery

Variable	Long COVID-19	No long COVID-19	p-value
Reinfection count	1.88±0.91	1.36±0.71	<0.001
Last infection <6 months	26 (32.5%)	200 (14.9%)	<0.001
COVID-19 ICU admission	7 (8.8%)	41 (3.1%)	0.008
Mechanical ventilation history	4 (5.0%)	17 (1.3%)	0.01
Vaccination doses	2.3±1.2	2.8±1.1	0.002

Values are presented as mean ± standard deviation or number(percentage). ICU: Intensive care unit; COVID: Coronavirus; COVID-19: Coronavirus disease-2019; SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2.

The present findings support a phenotype-based interpretation of perioperative long COVID risk. Patients with poor glycemic control, severe obesity, advanced coronary artery disease, frailty, neuropsychiatric or immunologic comorbidities, and recent infection were most likely to experience worsening of symptoms. These features define a clinically recognizable vulnerability pattern that may assist in preoperative counseling, optimization of metabolic parameters, and structured postoperative follow-up. Such an approach may be more informative than considering long COVID as a uniform perioperative condition.

Several limitations should be acknowledged. The study represents a retrospective analysis of prospectively collected registry data and therefore cannot establish causality. The absence of an off-pump comparator group limits the evaluation of bypass-specific effects. The symptom assessment tool, although applied prospectively, has not undergone external validation. Biomarkers reflecting endothelial dysfunction or autonomic imbalance were not available for mechanistic analysis. Finally, follow-up was limited to three months, and longer-term symptom trajectories remain uncertain.

Long COVID is present in a meaningful proportion of patients undergoing CABG with CPB, who have heterogeneous postoperative trajectories. Symptom worsening appears to be driven primarily by metabolic and neuropsychiatric vulnerabilities rather than by procedural exposure alone. CPB is generally well tolerated, and risk stratification based on

Table 7. Multivariable logistic regression analysis identifying predictors of clinically meaningful postoperative worsening of long COVID symptoms

Variable	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age ≥65 years	1.82 (1.01-3.29)	0.046	1.41 (0.74-2.68)	0.29
Female sex	2.12 (1.16-3.89)	0.014	1.76 (0.93-3.31)	0.08
BMI ≥36 kg/m²	3.89 (1.67-9.04)	0.002	3.21 (1.31-7.86)	0.011
HbA1c >9%	3.02 (1.54-5.92)	0.001	2.41 (1.32-4.38)	0.004
≥3-vessel coronary artery disease	2.27 (1.18-4.36)	0.014	1.94 (1.02-3.68)	0.043
Neurologic disease	3.18 (1.55-6.52)	0.002	2.48 (1.19-5.14)	0.016
Psychiatric disease	3.41 (1.73-6.72)	<0.001	2.63 (1.31-5.29)	0.006
Immunologic disease	3.72 (1.39-9.96)	0.009	2.71 (1.01-7.24)	0.047
Infection-to-surgery interval <6 months	3.05 (1.58-5.90)	0.001	2.36 (1.19-4.67)	0.014
CPB duration (per 10-min increase)	1.12 (1.01-1.25)	0.032	1.09 (1.00-1.21)	0.048
Frailty score ≥5	3.26 (1.68-6.32)	<0.001	2.58 (1.29-5.16)	0.007
Female sex × HbA1c interaction term	—	—	1.32 (0.74-2.36)	0.34

Clinically meaningful worsening was defined as an increase ≥5 points in the composite symptom score at three months. CPB duration was modeled per 10-minute increment.
OR: Odds ratio; CPB: Cardiopulmonary bypass; COVID: Coronavirus; BMI: Body mass index; CI: Confidence interval.

host-related factors may help guide perioperative management. Further multicenter studies incorporating objective neurocognitive assessment, biomarker profiling, and extended follow-up are warranted to refine perioperative risk stratification in patients with prior SARS-CoV-2 infection undergoing cardiac surgery.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Institutional Ethics Committee of Dr. İsmail Fehmi Cumalioğlu City Hospital (approval number: AN-261203-16, date: 12.03.2026).

Informed Consent: The ethics committee waived the requirement for informed consent because the study was observational.

Acknowledgments

The author would like to acknowledge Volkan Yurdakul, perfusionist at Dr. İsmail Fehmi Cumalioğlu City Hospital, for his contribution to the systematic recording and organization of intraoperative perfusion parameters. The author also thanks Hüseyin Anasız, cardiovascular surgeon at the same institution, for his support in the verification and structuring of operative data. In addition, sincere appreciation is extended to Aslı Özdemir Çınar, head ward nurse of the cardiovascular surgery clinic, for her assistance in coordinating in-hospital monitoring processes and postoperative follow-up assessments that contributed to the completeness of the clinical dataset.

For transparency, the author note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the author.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

REFERENCES

1. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27:601-15. doi: 10.1038/s41591-021-01283-z.
2. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;38:101019. doi: 10.1016/j.eclinm.2021.101019.
3. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53:737-54. doi: 10.1080/23744235.2021.1924397.
4. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. Nat Med. 2021;27:626-31. Erratum in: Nat Med. 2021;27:1116. doi: 10.1038/s41591-021-01361-2.
5. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020;324:603-5. doi: 10.1001/jama.2020.12603.
6. Evans RA, McAuley H, Harrison EM, Shikotra A, Singapuri A, Sereno M, et al.; PHOSP-COVID Collaborative Group. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021;9:1275-87. Erratum in: Lancet Respir Med. 2022;10:e9. Erratum in: Lancet Respir Med. 2024;12:e41. doi: 10.1016/S2213-2600(24)00142-5.
7. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. BMJ. 2020;370:m3026. doi: 10.1136/bmj.m3026.
8. Paneroni M, Simonelli C, Saleri M, Bertacchini L, Venturelli M, Troosters T, et al. Muscle performance and physical function in patients with COVID-19-associated pneumonia at hospital discharge. Eur J Phys Rehabil Med. 2021;57:1-8.
9. Fedorchenko Y, Zimba O. Long COVID in autoimmune rheumatic diseases. Rheumatol Int. 2023;43:1197-207. doi: 10.1007/s00296-023-05319-0.
10. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395:1417-8. doi: 10.1016/S0140-6736(20)30937-5.
11. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. Nat Med. 2022;28:583-90. doi: 10.1038/s41591-022-01689-3.

12. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5:1265-73. Erratum in: JAMA Cardiol. 2020;5:1308. doi: 10.1001/jamacardio.2020.4648.

13. Squiccimarro E, Labriola C, Malvindi PG, Margari V, Guida P, Visicchio G, et al. Prevalence and clinical impact of systemic inflammatory reaction after cardiac surgery. J Cardiothorac Vasc Anesth. 2019;33:1682-90. doi: 10.1053/j.jvca.2019.01.043.

14. McDonagh DL, Berger M, Mathew JP, Graffagnino C, Milano CA, Newman MF. Neurological complications of cardiac surgery. Lancet Neurol. 2014;13:490-502. doi: 10.1016/S1474-4422(14)70004-3.

15. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, et al.; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; Society of Cardiovascular Anesthesiologists; Society of Thoracic Surgeons. 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;58:e123-210. doi: 10.1016/j.jacc.2011.08.009.

16. Dobbs TD, Gibson JAG, Fowler AJ, Abbott TE, Shahid T, Torabi F, et al. Surgical activity in England and Wales during the COVID-19 pandemic: a nationwide observational cohort study. Br J Anaesth. 2021;127:196-204. doi: 10.1016/j.bja.2021.05.001.

17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The STROBE statement: guidelines for reporting observational studies. BMJ. 2007;335:806-8.

18. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV; WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22:e102-7. doi: 10.1016/S1473-3099(21)00703-9.

19. Predoi CE, Filipescu DC, Stefan MG, Iordache N. Elective cardiopulmonary bypass surgery after COVID-19: vasoactive needs and early complications. J Clin Med. 2025;14:8290. doi: 10.3390/jcm14238290.

20. Predoi CE, Dascalu A, Goicea R, Stefan M, Filipescu D, Iordache N, et al. Impact of COVID-19 history on perioperative outcomes: a systematic review. COVID. 2025;5:148. doi: 10.3390/covid5090148.

21. Şahin İ, Batur Ş, Üstündağ A, Arapi B, Tel Üstünışık Ç, Göksedef D, et al. The impact of COVID-19 on graft vasculopathy and postoperative thromboembolism in CABG patients: a prospective controlled study. Cardiovasc Toxicol. 2025;25:1123-38. doi: 10.1007/s12012-025-10017-3.