

Local Inflammation May Underlie Cardiac Damage in Post-COVID-19 Period

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Abstract

Background: Some patients experience subclinical cardiovascular dysfunction after COVID-19, possibly driven by persistent inflammatory mechanisms that remain incompletely understood. NT-proBNP and GDF-15 have been proposed as biomarkers of myocardial stress and inflammation in this context.

Objectives: To investigate associations between NT-proBNP, GDF-15, inflammatory cytokines, and echocardiographic parameters in patients with Post-COVID-19 Condition (PCC).

Methods: This cross-sectional study included 78 adults followed in a university hospital cohort. Participants were stratified into elevated NT-proBNP (n = 39) and normal NT-proBNP (n = 39) groups. Clinical, laboratory, and echocardiographic variables were assessed, including PALS and RV-GLS. Serum GDF-15 and cytokines were quantified using a multiplex bead assay. ROC curve analysis evaluated the predictive value of GDF-15 for elevated NT-proBNP.

Results: Participants with elevated NT-proBNP had reduced PALS (28.5% vs. 36.7%; $p < 0.05$), and higher GDF-15 (median 368 vs. 219 pg/mL) and IL-1 β levels (2.47 vs. 0.94 pg/mL; $p < 0.05$). GDF-15 ≥ 519 pg/mL predicted elevated NT-proBNP (AUC = 0.65). Individuals with elevated GDF-15 also showed worse RV-GLS (20.2% vs. 26.9%; $p < 0.05$) and higher IL-8 levels ($p < 0.05$).

Conclusions: NT-proBNP, GDF-15, and IL-1 β identify subclinical myocardial dysfunction in PCC, supporting a pathophysiological model centered on persistent inflammation and early myocardial remodeling, distinct from classic ischemic pathways.

Keywords: COVID-19; Growth Differentiation Factor 15; Inflammation; Echocardiography.

Introduction

After an episode of SARS-CoV-2 infection, patients may develop long-lasting cardiovascular symptoms¹ and persistently elevated biomarkers of myocardial injury.² However, the underlying pathophysiological mechanisms remain incompletely understood.

Systemic inflammation has been correlated with N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) elevations and increased mortality in this context.³ It has been suggested that persistent cardiac dysfunction following COVID-19 may be associated with local activation of immune and inflammatory pathways, ultimately leading to myocardial injury.²

GDF-15, a cytokine related to the TGF- β family, is an important prognostic biomarker in inflammation and cardiovascular disease. Elevated levels have been linked to hypoxemia, SARS-CoV-2 viremia, and adverse outcomes. As a marker of myocardial stress and remodeling, GDF-15 may also contribute to autonomic dysfunction and subclinical heart failure in COVID-19, reinforcing its relevance among emerging biomarkers.⁴

Previous studies indicate that up to 36% of patients hospitalized with COVID-19 present elevated NT-proBNP

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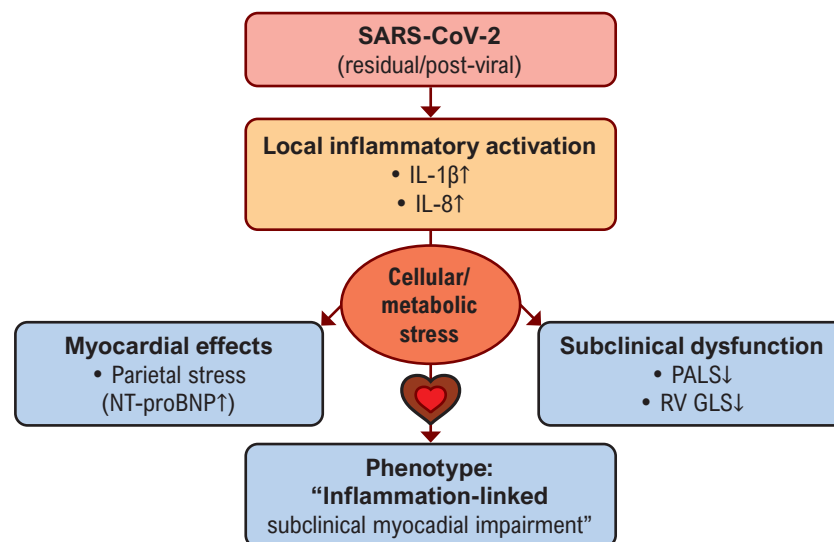
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Central Illustration: Local Inflammation May Underlie Cardiac Damage in Post-COVID-19 Period


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Proposed Pathophysiological Model


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Proposed pathophysiological model of inflammation-linked subclinical myocardial dysfunction in the post-COVID-19 period. Schematic representation of the proposed mechanism linking residual or post-viral SARS-CoV-2 effects to local inflammatory activation (IL-1 β and IL-8), cellular and metabolic stress, myocardial wall stress with NT-proBNP elevation, and early subclinical cardiac dysfunction, reflected by impaired left atrial strain (PALS) and right ventricular global longitudinal strain (RV GLS).

levels, a well-established marker of cardiac distress. Inflammatory cytokines such as IL-6, TNF- α , and IL-1 β have also been associated with the progression of post-COVID-19 condition (PCC).⁵ However, the roles of NT-proBNP and GDF-15 in this setting have not yet been fully explored. The relationship between inflammation, cardiac stress markers, and subclinical myocardial impairment in PCC therefore remains unclear.

In this study, we analyzed serum levels of GDF-15, NT-proBNP, inflammatory cytokines, and echocardiographic parameters in a cohort of patients who survived the acute phase of COVID-19. The objective was to investigate the relationship between systemic inflammation and persistent alterations in cardiac structure or function, thereby providing insights into the mechanisms underlying heart involvement in the post-COVID-19 period.

Methods

Ethical approval

The study was approved by the Research Ethics Committee of a local tertiary university hospital (CAAE: 59213722.5.0000.5243). In accordance with ethical standards, written informed consent was obtained from all participants.

Study design and participant selection

This study represents a cross-sectional analysis of data collected from 144 adult patients recruited between July 2022 and July 2023, all of whom had at least one positive polymerase chain reaction (PCR) test for SARS-CoV-2 during the COVID-19 pandemic.

Participants were enrolled in the post-COVID-19 period to investigate PCC at a tertiary care university hospital in Brazil. Upon enrollment, they followed a standardized study protocol that included cardiology evaluations at baseline and every six months, as well as laboratory testing at baseline and one year after the initial blood collection.

For the present analysis, we initially identified a subgroup of participants ($n = 39$) who exhibited elevated NT-proBNP levels at baseline laboratory evaluation, according to the cutoff recommended by the Heart Failure Association of the European Society of Cardiology. A control group of 39 individuals from the same cohort with normal NT-proBNP levels was then selected using a 1:1 matching ratio. Matching was performed based on sex, age, and the presence of relevant comorbidities (diabetes and hypertension) to minimize potential confounding in the comparison between groups.

Clinical variables

Social and demographic information, past medical history, and current medications were obtained through patient interviews and medical record review. Body mass index (BMI) was measured at study entry. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m², calculated using the CKD-EPI creatinine equation (2021). Acute heart failure was diagnosed according to the Framingham Heart Failure criteria, applied at each cardiology consultation.⁶⁻⁸

Echocardiographic variables

Transthoracic echocardiography was performed using a commercially available system (EPIQ CVx®, Philips, Amsterdam, The Netherlands) following the American Society of Echocardiography (ASE) protocol for chamber quantification,⁹ Doppler analysis, and assessment of Peak Left Atrial Strain (PALS) and biventricular strain. All examinations were reviewed by a cardiologist specialized in echocardiographic analysis who was blinded to participants' clinical and laboratory data.

The following echocardiographic parameters were evaluated: Left Ventricular Ejection fraction (LVEF): measured using the Simpson biplane method from apical four- and two-chamber views; PALS, obtained via speckle-tracking echocardiography from apical four-chamber views, representing the reservoir function of the left atrium; and Right Ventricular Global Longitudinal Strain (RV-GLS), calculated from focused right ventricular apical four-chamber views using speckle-tracking analysis, reflecting right ventricular systolic function. Echocardiographic variables were reported as continuous measures and compared between groups.

Laboratory variables

Peripheral blood samples were collected in the morning, and serum samples were stored frozen for subsequent analysis. NT-proBNP concentrations were measured by automated chemiluminescent immunoassay using the Alinity C system (Abbott®, Brazil) at the Clinical Analysis and Pathology Unit of the university hospital. Age-adjusted NT-proBNP cut-off values were applied (<50 years: 125 pg/mL; 50–75 years: 250 pg/mL; >75 years: 500 pg/mL).

Additional adjustments were made according to renal function and BMI, as previously described: NT-proBNP cut-off increased by 15%, 25%, and 35% for estimated glomerular filtration rates of 45–60, 30–45, and <30 mL/min/1.73 m², respectively. NT-proBNP cut-off reduced by 25%, 30%, and 40% for BMI values of 30–35, 35–40, and >40 Kg/m², respectively.⁶ Serum levels of growth differentiation factor 15 (GDF-15) were measured using commercially available immunoassays (R&D Systems, USA). Absorbance values were read with the Spectramax M3 Multi-Mode Microplate Reader (Molecular Devices, USA).

A multiplex bead assay was performed to quantify serum levels of chemokines and cytokines (Bio-Plex Magpix®, Biorad Laboratories, USA), as previously described.¹⁰ Serum levels of 27 biomarkers were analyzed: chemokine monocyte chemoattractant protein 1 (MCP-1/CCL-2); macrophage

inflammatory protein 1α (MIP-1α/CCL-3); macrophage inflammatory protein 1β (MIP-1β/CCL-4); chemokine C-C ligand 5 (RANTES/CCL-5); chemokine C-C ligand 11 (eotaxin-1/CCL-11); interferon gamma-induced protein 10 (IP-10/CXCL-10); granulocyte-macrophage colony-stimulation factor (GM-CSF/CSF-2); granulocyte colony-stimulating factor (G-CSF/CSF-3); basic fibroblast growth factor (FGFb); interferon γ (IFN-γ); interleukin 1 receptor antagonist (IL-1ra); interleukin 1β (IL-1β); IL-2, -4, -5, -6, -7, -8 (CXCL-8), -9, -10, -12p70, -13, -15, and -17; platelet-derived growth factor BB (PDGF-BB), tumor necrosis factor (TNF), and Vascular Endothelial Growth Factor (VEGF).

Statistical analysis

Normality of continuous data was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median and interquartile range (IQR) or mean and standard deviation (SD), depending on data distribution. Between-group comparisons were performed using the Student's t-test or, alternatively, the Mann–Whitney U test. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. Given the evaluation of 19 cytokines, p-values from between-group comparisons were adjusted for multiple testing using the Benjamini–Hochberg false discovery rate (FDR) procedure. An FDR-adjusted p < 0.05 was considered statistically significant.

Variables with p < 0.20 in univariate analyses, or those considered biologically relevant (age, sex, BMI, hypertension, diabetes), were included as candidate predictors in multivariable logistic regression models. Age and sex were forced into all models irrespective of univariate significance. Parsimonious models were applied to maintain adequate events-per-variable ratios. Receiver operating characteristic (ROC) curve analysis was used to assess whether cytokine levels could predict elevated NT-proBNP levels. Categorized cytokine levels were used to improve model performance in regression analyses.

The sample size was determined by feasibility during the recruitment period of the prospective cohort; therefore, no formal a priori sample size calculation was performed. Given the fixed sample size and the exploratory nature of the study, emphasis was placed on effect sizes and 95% confidence intervals for interpretation of results. In addition, a post-hoc power analysis was conducted for the primary comparison of GDF-15 levels between patients with elevated versus normal NT-proBNP, using the observed effect size and a two-sided α of 0.05. All statistical analyses were conducted using R software (RStudio, version 2024.03.1+402).

Results

Figure 1 presents the flowchart of participant selection for the 78 individuals included in the analysis. Baseline characteristics are summarized in Table 1. The study population was predominantly female, with a median age of 60 years, and showed a high prevalence of hypertension, dyslipidemia, and diabetes.

When comparing groups stratified by NT-proBNP levels, a consistent pattern of greater myocardial stress and

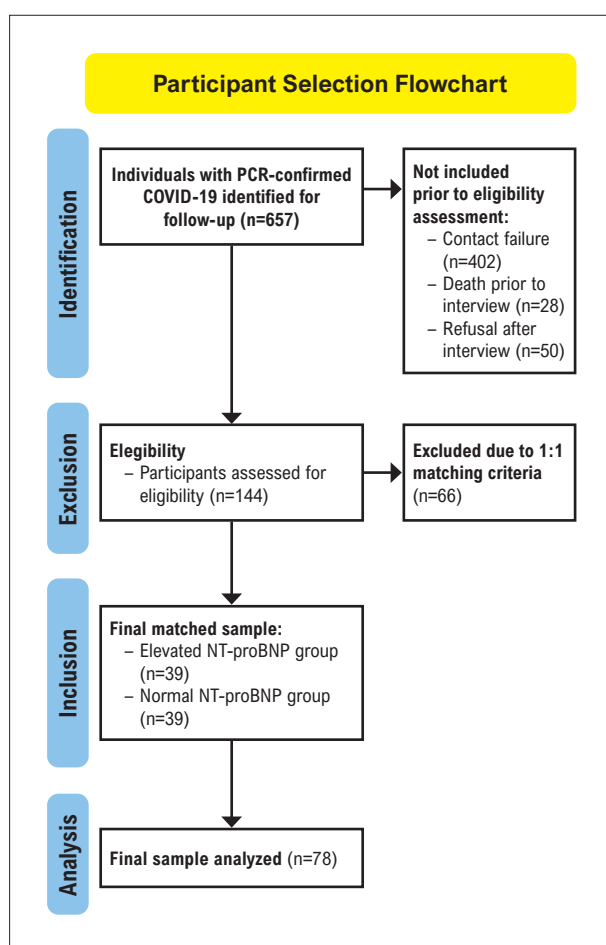


Figure 1 – Flowchart of Participant Selection and Inclusion Criteria Based on NT-proBNP Levels in Post-COVID-19 Patients.

inflammation was observed among individuals with elevated biomarker values. These participants exhibited impaired atrial function (reduced PALS) and right ventricular function (reduced RV-GLS), along with higher concentrations of GDF-15 and IL-1 β . They also had a higher frequency of hospitalization during the acute phase of COVID-19. Additional clinical and laboratory parameters are detailed in Table 1.

In predictive analyses, GDF-15 demonstrated moderate performance in distinguishing participants with elevated NT-proBNP (AUC = 0.65). The optimal cutoff value identified was 519 pg/mL. Based on this threshold, participants were categorized into elevated and normal GDF-15 groups, as shown in Table 2. Individuals with elevated GDF-15 levels were older, had a greater burden of comorbidities, and exhibited worse right ventricular strain and higher IL-8 concentrations. These findings suggest an interaction between local inflammation, cellular stress, and subclinical dysfunction. No significant differences were observed between groups for most of the other inflammatory biomarkers evaluated.

Because 19 cytokines were analyzed, p-values were adjusted for multiple testing using the Benjamini–Hochberg

false discovery rate. Although GDF-15 and IL-1 β showed nominal significance in unadjusted analyses ($p = 0.030$ and $p = 0.029$, respectively), none of the cytokines remained statistically significant after FDR correction (all adjusted $p \geq 0.28$). Therefore, cytokine analyses should be interpreted as exploratory (Supplementary Table 1).

A post-hoc power analysis for the comparison of GDF-15 levels between elevated and normal NT-proBNP groups demonstrated 77.1% power (Cohen's $d = 0.42$; $\alpha = 0.05$). In contrast, the analysis based on the ROC-derived GDF-15 cut-off yielded only 43.7% power, indicating limited ability to detect differences in this secondary, dichotomized comparison.

In multivariable logistic regression models, high GDF-15 was independently associated with elevated NT-proBNP (adjusted OR 6.95, 95% CI 1.79–33.32; $p = 0.008$). Similarly, high IL-1 β showed a strong independent association with elevated NT-proBNP (adjusted OR 7.04, 95% CI 2.11–28.46; $p = 0.007$) (Table 3).

Discussion

Evidence indicates that cardiac injury in patients with COVID-19 can occur even in the absence of direct viral tropism to cardiac tissue, suggesting an immune-mediated mechanism.^{10,11} In line with this, our group previously hypothesized that a sustained inflammatory axis – driven by macrophage dysfunction and cytokine responses – may play a key role in perpetuating myocardial damage in the post-COVID-19 period. Additionally, Sabanoglu et al.¹² suggested that NT-proBNP and high-sensitivity troponin could predict long-term outcomes in COVID-19, underscoring the prognostic relevance of cardiac biomarkers in this setting.

In the present study, our findings support the hypothesis that a local inflammatory response, rather than a diffuse systemic reaction, may underlie subclinical myocardial involvement in the post-COVID-19 period. Patients with elevated NT-proBNP levels exhibited significantly higher IL-1 β concentrations (median 5.2 pg/mL) compared with those with normal NT-proBNP (median 3.1 pg/mL, $p = 0.029$), suggesting persistence of local inflammation. Other classical pro-inflammatory cytokines, including IL-6 and TNF- α , did not differ significantly between groups ($p = 0.12$ and $p = 0.695$, respectively), reinforcing the concept of selective activation of the inflammasome–IL-1 β axis.

Additionally, levels of GDF-15, a recognized biomarker of cellular stress, mitochondrial dysfunction, and low-grade inflammation,^{13–15} were significantly higher in the elevated NT-proBNP group (median 367.8 pg/mL) compared with the normal NT-proBNP group (median 219.1 pg/mL, $p = 0.030$). Notably, 41% of individuals with elevated NT-proBNP also presented high GDF-15 levels, compared with 12.8% in the control group ($p = 0.011$). This finding reinforces the role of GDF-15 as a marker of cardiovascular stress and a potential integrator of inflammatory and metabolic pathways in post-COVID-19 pathophysiology, consistent with previous reports.¹⁴

The Central Illustration summarizes the proposed pathophysiological mechanism, integrating persistent

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Table 1 – Baseline characteristics of the studied population

	Overall (N = 78)	Elevated NT-proBNP (N = 39)	Normal NT-proBNP (N = 39)
Age (Years)^a	61 [52; 71]	64 [54; 71]	57 [49; 68]
Male sex	26 (33.3)	14 (35.9)	12 (30.8)
Body mass index (kg/m²)^a	28 [25; 32]	28 [24; 32]	29 [26; 32]
Hypertension	55 (70.5)	26 (66.7)	29 (74.4)
Diabetes	28 (35.9)	15 (38.5)	13 (33.3)
Dyslipidemia	42 (53.8)	22 (56.4)	20 (51.3)
Chronic kidney disease	26 (33.3)	16 (41.0)	10 (25.6)
Chronic heart failure	17 (23.9)	12 (30.7)	5 (12.8)
Acute heart failure	12 (15.4)	7 (17.9)	5 (12.8)
Echocardiogram			
LVEF ^a	60.0 [57.3; 64.6]	59.0 [52.9; 63.5]	61.8 [60.0; 65.5]
PALS ^a	32.0 [25.4; 38.5]	28.50 [23.0; 33.5]	36.7 [30.1; 40.3] *
RV GLS ^a	23.7 [21.5; 28.7]	22.7 [19.5; 27.3]	27.6 [21.8; 29.8]
Cytokines (pg/mL)			
GDF-15 ^a	291 [161; 578]	368 [14; 855]	219 [129; 437] *
IL-1β ^a	2.47 [0.94; 4.14]	2.47 [0.94; 4.14]	0.94 [0.75; 2.47] *
> 1 COVID-19 episode	19 (24.4)	5 (12.8)	14 (35.9)*
Hospitalization (n=64)	37 (57.8)	21 (56.7)	7 (25.9)*
Vaccines ^b			
No dose	4 (6.3)	4 (100.0)	0 (0.0)
1 dose	3 (4.7)	3 (100.0)	0 (0.0)
2 doses	12 (18.2)	6 (50.0)	6 (50.0)
3 doses	11 (16.7)	6 (54.5)	5 (45.5)
4 doses	30 (45.4)	17 (56.7)	13 (43.3)

Data presented as n (%), unless otherwise specified. *a* median [IQR]; LVEF: left ventricular ejection fraction; PALS: peak atrial longitudinal strain; RV GLS: right ventricular global longitudinal strain; GDF: growth differentiation factor; IL-1β: Interleukin 1 beta; *b* Before enrollment. * *p*-value < 0.05.

inflammasome activation, myocardial stress signaling, and early atrial and right ventricular dysfunction in the post-COVID-19 period.

Moreover, participants with elevated GDF-15 levels exhibited higher IL-8 concentrations (14.63 vs. 9.61 pg/mL, *p* < 0.05), a chemokine involved in neutrophil recruitment and endothelial signaling. IL-8 is stimulated by inflammatory mediators such as TNF-α and IL-6,^{15,16} as well as by extracellular stressors including hypoxia and oxidative stress,¹⁷ suggesting a potential relationship between GDF-15 and IL-8 in the context of inflammation and extracellular matrix remodeling following injury. Although its precise role in this setting remains to be fully clarified, this finding may indicate a broader inflammatory response.

Patients with elevated GDF-15 also demonstrated significantly reduced right ventricular global longitudinal strain, indicative of incipient subclinical dysfunction. This impairment may reflect persistent hemodynamic burden, pulmonary vascular remodeling, or endothelial inflammation, particularly among individuals with cardiometabolic comorbidities. Such findings reinforce the hypothesis that cardiac involvement in the post-COVID-19 period may encompass distinct myocardial patterns, including isolated right ventricular impairment.

In parallel, PALS/LASr was markedly reduced in participants with elevated NT-proBNP (median 25.10%) compared with controls (median 31.90%; *p* = 0.027), indicating subclinical atrial dysfunction. Previous studies have identified left atrial reservoir strain as a sensitive marker of early atrial impairment, inversely correlated with natriuretic peptide levels, even in the absence of overt cardiac disease.¹⁸ These findings suggest early myocardial remodeling, likely mediated by sustained inflammation, endothelial dysfunction, and chronic hemodynamic stress. Importantly, our results are consistent with prior evidence:¹⁹ in individuals without comorbidities assessed between four and twelve weeks after SARS-CoV-2 infection, symptomatic patients – particularly those with dyspnea and exercise intolerance – demonstrated significant reductions in left atrial strain compared with asymptomatic individuals.¹⁹

The increase in cardiac biomarkers observed in the post-COVID-19 period may indicate that inflammatory mechanisms, rather than classical myocardial ischemia, contribute to cardiac damage in this setting. GDF-15 emerges as a marker of inflammation, cellular stress, and mitochondrial dysfunction, and may prove useful for cardiovascular risk stratification. Interestingly, individuals with elevated NT-proBNP reported fewer recurrent episodes of COVID-19 but had higher hospitalization rates. This observation suggests that the severity of the acute episode, rather than its frequency, may play a more decisive role in driving long-term cardiac involvement.

It is noteworthy that unvaccinated and single-dose vaccinated participants were found only in the group with elevated NT-proBNP, suggesting that incomplete vaccination may be associated with increased post-COVID-19 cardiac stress.²⁰ However, further studies are required to investigate this hypothesis more thoroughly.

Table 2 – Comparison of clinical, echocardiographic, and inflammatory characteristics between elevated and normal GDF-15 groups

	Elevated GDF-15 (N = 21)	Normal GDF-15 (N = 57)
Age (Years) ^a	65 [58; 77]	59 [49; 66] *
Male sex	11 (52.4)	15 (26.3)
BMI (kg/m ²) ^a	27 [23; 31]	29 [27; 33] *
Hypertension	18 (85.7)	37 (64.9)
Diabetes	14 (66.7)	14 (24.6) *
Dyslipidemia	9 (42.9)	33 (57.9)
Chronic kidney disease	14 (66.6)	12 (21.0) *
Chronic heart failure	6 (30.0)	11 (21.6)
Acute heart failure	4 (14.0)	8 (17.0)
Echocardiogram		
LVEF ^a	60.0 [52.4; 60.0]	62.2 [58.0; 65.1]
PALS ^a	30.0 [28.0; 31.1]	33.6 [25.4; 40.1]
RV GLS ^a	20.2 [17.7; 22.4]	26.9 [22.1; 29.8] *
Cytokines (pg/mL)		
IL-1β ^a	2.47 [0.94; 4.14]	1.17 [0.94; 2.51]
IL-6 ^a	11.18 [9.00; 15.30]	2.67 [0.96; 5.13]
IFNγ ^a	18.3 [15.4; 22.3]	14.4 [10.8; 20.3]
FGFb ^a	42.8 [35.0; 44.3]	35.1 [26.9; 42.8]
PDGFbb ^a	1.522 [766; 3.613]	2.783 [1.787; 4.390]
IL-8 ^a	14.6 [10.2; 27.2]	9.6 [6.0; 14.6]*
GCSF ^a	119 [100; 174]	90 [60; 124]
> 1 COVID-19 episode	3 (14.3)	16 (28.1)
Symptomatic COVID-19	16 (76.2)	48 (84.2)

^amedian [IQR]; LVEF: left ventricular ejection fraction; PALS: peak atrial longitudinal strain; RV GLS: right ventricular longitudinal strain, IL: Interleukin; IFNγ: interferon-gamma; FGFb: fibroblast growth factor basic; PDGFbb: Platelet-Derived Growth Factor-BB; GCSF: Granulocyte Colony-Stimulating Factor. * p-value < 0.05.

This study is original in demonstrating that the combined assessment of NT-proBNP, GDF-15, and IL-1β may characterize subclinical myocardial dysfunction, reinforcing a pathophysiological model based on chronic inflammation. This model differs from the classic ischemic paradigm and aligns with mechanisms described in heart failure with preserved ejection fraction. In this context, integrated evaluation of

Table 3 – Multivariable logistic regression models for elevated NT-proBNP

Variable	Adjusted OR	95% CI (Lower-Upper)
Model 1 – Predictor: High GDF-15		
High GDF-15 (vs. low)	*6.95	1.79 – 33.32
Age (years)	1.03	1.00 – 1.08
Male sex	0.98	0.30 – 3.14
BMI (kg/m ²)	1.08	0.98 – 1.19
Hypertension	*0.25	0.06 – 0.94
Diabetes	0.90	0.25 – 3.02
Chronic kidney disease	1.28	0.36 – 4.50
Model 2 – Predictor: High IL-1β		
High IL-1β (vs. low)	*7.04	2.11 – 28.46
Age (years)	1.04	1.00 – 1.08
Male sex	0.85	0.24 – 2.85
BMI (kg/m ²)	1.07	0.97 – 1.18
Hypertension	*0.18	0.04 – 0.71
Diabetes	1.78	0.54 – 6.17
Chronic kidney disease	2.04	0.60 – 7.33
Model 1 – Predictor: High GDF-15		
High GDF-15 (vs. low)	*6.95	1.79 – 33.32
Age (years)	1.03	1.00 – 1.08
Male sex	0.98	0.30 – 3.14
BMI (kg/m ²)	1.08	0.98 – 1.19
Hypertension	0.25	0.06 – 0.94

Multivariable logistic regression models assessing independent predictors of elevated NT-proBNP. Model 1 evaluates high GDF-15; Model 2 evaluates high IL-1β. Both models were adjusted for demographic and clinical confounders (age, sex, BMI, hypertension, diabetes, and chronic kidney disease). Data are expressed as adjusted odds ratios with 95% confidence intervals. * p-value < 0.05.

cardiac involvement in the post-COVID-19 period would benefit from monitoring these biomarkers.

The study has some limitations, including the relatively small sample size and the absence of cardiac magnetic resonance imaging to assess myocardial fibrosis. Nonetheless, it contributes to the assessment and monitoring of cardiac stress and proposes an integrative model of myocardial injury in the post-COVID-19 period, with clinical applicability and potential scientific relevance. The relatively small sample size of the matched subgroups (39 vs. 39) limits statistical power, particularly for multivariable analyses and dichotomized biomarkers, increasing the risk of type II error. The sample size was determined by feasibility during the pandemic, and no formal *a priori* calculation was performed; therefore, our post-hoc power estimates ($\approx 77\%$ for the continuous GDF-15 comparison and $\approx 44\%$ for the ROC-based cut-off) should be interpreted as descriptive. In addition, the single-center design and 1:1 matching may have introduced selection bias and reduced generalizability. Finally, the cross-sectional nature of the analysis precludes causal inferences regarding the relationship between inflammation, cellular stress, and subclinical myocardial dysfunction.

Nonetheless, the study provides meaningful evidence for the evaluation of cardiac stress in the post-COVID-19 context and proposes an integrative model of myocardial injury with potential clinical and scientific relevance. These findings underscore the need for longitudinal studies and broader imaging availability to further clarify mechanisms and prognostic implications.

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References

1. World Health Organization. Post COVID-19 Condition (Long COVID) [Internet]. Geneva: WHO; 2022 [cited 2026 Mar 17]. Available from: <https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition>.
2. Carvalho M, Lagoeiro A. Biomarkers and Mononuclear Inflammatory Activity in COVID-19 Survivors. *Int J Cardiovasc Sci*. 2024;37:e20240016. doi: 10.36660/ijcs.20240016.
3. Lionte C, Sorodoc V, Haliga RE, Bologa C, Ceasovschiu A, Petris OR, et al. Inflammatory and Cardiac Biomarkers in Relation with Post-Acute COVID-19 and Mortality: What We Know after Successive Pandemic Waves. *Diagnostics*. 2022;12(6):1373. doi: 10.3390/diagnostics12061373.
4. Nyárády BB, Kiss LZ, Bagyura Z, Merkely B, Dósa E, Láng O, et al. Growth and Differentiation Factor-15: A Link between Inflammation and Cardiovascular Disease. *Biomed Pharmacother*. 2024;174:116475. doi: 10.1016/j.biopha.2024.116475.
5. Alonso-Domínguez J, Gallego-Rodríguez M, Martínez-Barros I, Calderón-Cruz B, Leiro-Fernández V, Pérez-González A, et al. High Levels of IL-1 β , TNF- α and MIP-1 α One Month after the Onset of

Author Contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Carvalho MRM, Rosário NF, Lugon JR; Acquisition of data: Carvalho MRM, Azevedo CRA, Ribeiro ML, Oliveira EM, Souza RVO, Castro MJC; Analysis and interpretation of the data: Carvalho MRM, Rosário NF, Ramos A, Lomba GSB, Lugon JR; Statistical analysis: Ramos A, Lomba GSB; Obtaining financing: Rosário NF, Lugon JR; Writing of the manuscript: Carvalho MRM, Rosário NF, Lomba GSB, Lugon JR.

Potential Conflict of Interest

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Universidade Federal Fluminense under the protocol number CAAE: 59213722.5.0000.5243. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

- the Acute SARS-CoV-2 Infection, Predictors of Post COVID-19 in Hospitalized Patients. *Microorganisms*. 2023;11(10):2396. doi: 10.3390/microorganisms11102396.
6. Bayes-Genis A, Docherty KF, Petrie MC, Januzzi JL, Mueller C, Anderson L, et al. Practical Algorithms for Early Diagnosis of Heart Failure and Heart Stress Using NT-proBNP: A Clinical Consensus Statement from the Heart Failure Association of the ESC. *Eur J Heart Fail*. 2023;25(11):1891-8. doi: 10.1002/ehf.3036.
7. Lu S, Robyak K, Zhu Y. The CKD-EPI 2021 Equation and Other Creatinine-Based Race-Independent eGFR Equations in Chronic Kidney Disease Diagnosis and Staging. *J Appl Lab Med*. 2023;8(5):952-61. doi: 10.1093/jalm/jfad047.
8. MDCalc. Framingham Heart Failure Diagnostic Criteria [Internet]. New York: MDCalc; 2025 [cited 2026 Mar 17]. Available from: <https://www.mdcalc.com/calc/3800/framingham-heart-failure-diagnostic-criteria>.
9. Lang RM, Badano LP, Mor-Avi V, Afzalalo J, Armstrong A, Ernande L, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular

- Imaging. *J Am Soc Echocardiogr.* 2015;28(1):1-39.e14. doi: 10.1016/j.echo.2014.10.003.
10. Saraiva GN, Rosário NF, Medeiros T, Leite PEC, Lacerda GS, Andrade TG, et al. Restoring Inflammatory Mediator Balance after Sofosbuvir-Induced Viral Clearance in Patients with Chronic Hepatitis C. *Mediators Inflamm.* 2018;2018:8578051. doi: 10.1155/2018/8578051.
 11. Mezache L, Nuovo GJ, Suster D, Tili E, Awad H, Radwański PB, et al. Histologic, Viral, and Molecular Correlates of Heart Disease in fatal COVID-19. *Ann Diagn Pathol.* 2022;60:151983. doi: 10.1016/j.anndiagpath.2022.151983.
 12. Sabanoglu C, Inanc IH, Polat E, Peker SA. Long-Term Predictive Value of Cardiac Biomarkers in Patients with COVID-19 Infection. *Eur Rev Med Pharmacol Sci.* 2022;26(17):6396-403. doi: 10.26355/eurev_202209_29667.
 13. di Candia AM, de Avila DX, Moreira GR, Villacorta H, Maisel AS. Growth Differentiation Factor-15, a Novel Systemic Biomarker of Oxidative Stress, Inflammation, and Cellular Aging: Potential Role in Cardiovascular Diseases. *Am Heart J Plus.* 2021;9:100046. doi: 10.1016/j.ahjo.2021.100046.
 14. May BM, Pimentel M, Zimerman LI, Rohde LE. GDF-15 as a Biomarker in Cardiovascular Disease. *Arq Bras Cardiol.* 2021;116(3):494-500. doi: 10.36660/abc.20200426.
 15. Strieter RM, Kunkel SL, Showell HJ, Remick DG, Phan SH, Ward PA, et al. Endothelial Cell Gene Expression of a Neutrophil Chemotactic Factor by TNF-alpha, LPS, and IL-1 Beta. *Science.* 1989;243(4897):1467-9. doi: 10.1126/science.2648570.
 16. Matsushima K, Oppenheim JJ. Interleukin 8 and MCAF: Novel Inflammatory Cytokines Inducible by IL 1 and TNF. *Cytokine.* 1989;1(1):2-13. doi: 10.1016/1043-4666(89)91043-0.
 17. Shi Q, Le X, Wang B, Xiong Q, Abbruzzese JL, Xie K. Regulation of Interleukin-8 Expression by Cellular pH in Human Pancreatic Adenocarcinoma Cells. *J Interferon Cytokine Res.* 2000;20(11):1023-8. doi: 10.1089/10799900050198471.
 18. Varadarajan V, Ambale-Venkatesh B, Hong SY, Habibi M, Ashikaga H, Wu CO, et al. Association of Longitudinal Changes in NT-proBNP with Changes in Left Atrial Volume and Function: MESA. *Am J Hypertens.* 2021;34(6):626-35. doi: 10.1093/ajh/hpab018.
 19. ZeinElabdeen SG, Sherif A, Kandil NT, Altabib AMO, Abdelrashid MA. Left Atrial Longitudinal Strain Analysis in Long Covid-19 Syndrome. *Int J Cardiovasc Imaging.* 2023;39(5):939-44. doi: 10.1007/s10554-023-02801-5.
 20. Parodi JB, Indavere A, Jacob PB, Toledo GC, Micali RG, Waisman G, et al. Impact of COVID-19 Vaccination in Post-COVID Cardiac Complications. *Vaccine.* 2023;41(8):1524-8. doi: 10.1016/j.vaccine.2023.01.052.

*Supplemental Materials

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