

Association of galectin-3 with echocardiographic parameters in acute COVID-19 heart failure phenotypes and a post-acute comparator cohort

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ABSTRACT

Background: Galectin-3 is involved in inflammatory and fibrotic pathways and may reflect myocardial remodeling in COVID-19. Its relationship with echocardiographic findings across heart failure phenotypes during acute disease and the post-acute period remains incompletely defined. This study aimed to examine associations between circulating galectin-3 and echocardiographic parameters in acute COVID-19 heart failure phenotypes and in a post-acute comparator group.

Methods: This single-center retrospective observational study included 86 participants: 61 adults assessed during hospitalization for acute COVID-19 and 25 adults assessed approximately 2 months after infection. The acute-phase participants were classified as HFrEF (n=6), HFmrEF (n=20), or HFpEF (n=35); the post-acute participants formed a separate comparator group (n=25). Between-group comparisons were recalculated from reported group sample sizes, means, and standard deviations using Welch analysis of variance with Games-Howell post hoc tests. Associations were summarized using reported Spearman correlation coefficients.

Results: Galectin-3 differed among the four analytical groups (Welch $p<0.001$). Games-Howell pairwise differences were observed between HFrEF and HFpEF ($p=0.027$), HFrEF and the post-acute comparator ($p=0.009$), HFmrEF and HFpEF ($p=0.019$), and HFmrEF and the post-acute comparator ($p<0.001$). In HFpEF, galectin-3 correlated with left atrial volume ($\rho=0.538$, $p<0.001$) and left atrial volume index ($\rho=0.532$, $p=0.001$). In the post-acute comparator, galectin-3 correlated inversely with LVEF ($\rho=-0.501$, $p=0.011$) and positively with E/e' ($\rho=0.525$, $p=0.007$) and LVESV ($\rho=0.535$, $p=0.006$). Large correlations in HFrEF were based on only six participants and were considered unstable.

Conclusions: Galectin-3 was associated with selected echocardiographic measures in this exploratory cohort. The small, uneven groups, absence of a robust adjusted model, and lack of longitudinal outcomes preclude conclusions regarding independent, prognostic, or phenotype-specific clinical utility.

Keywords: COVID-19, echocardiography, galectin-3, heart failure phenotypes, post-acute COVID-19

Received: 19 April 2026; Accepted: 17 June 2026; Published: 30 June 2026.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a multisystem disorder in which cardiovascular involvement plays a major role in clinical severity and outcomes. Cardiac manifestations range from mild myocardial injury to severe heart failure (HF), substantially increasing the risk of adverse outcomes and mortality [1,2,3]. HF is also a common pre-existing condition among hospitalized patients with COVID-19, with a reported prevalence of 4.9% to 13%, and is consistently associated with poorer prognosis and increased risk of death [4,5,6,7].

The cardiovascular effects of COVID-19 may differ between the acute and post-acute phases of the disease. Available evidence suggests that diastolic dysfunction and right ventricular (RV) impairment may be more frequent than conventional systolic dysfunction in patients with COVID-19 [8]. Post-acute sequelae of SARS-CoV-2 infection (PASC), commonly referred to as Long COVID, encompass persistent symptoms and organ abnormalities after the acute phase. Current definitions distinguish ongoing symptomatic COVID-19 (4–12 weeks) from post-COVID-19 syndrome (>12 weeks) [9]. Because the comparator cohort in this study was assessed approximately

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2 months after infection, it is referred to as the post-acute COVID-19 comparator; this terminology does not imply a diagnosis of post-COVID-19 syndrome.

Cardiovascular manifestations are among the most important features of PASC. A meta-analysis including 37 studies and nearly 3 million individuals showed that survivors of COVID-19 were four times more likely to experience chest pain and three times more likely to report palpitations than uninfected individuals, while approximately 15% developed persistent cardiovascular sequelae [10]. Similarly, the World Heart Federation Global COVID-19 Study, which followed 2,535 hospitalized adults across 16 countries, emphasized the importance of long-term cardiovascular risk assessment and follow-up, particularly in resource-limited settings [11].

Myocardial fibrosis is a central mechanism in the development and progression of HF. Galectin-3 (Gal-3), a beta-galactoside-binding lectin, has emerged as an important biomarker because of its involvement in inflammatory and fibrotic pathways. Elevated Gal-3 levels have been associated with cardiovascular injury and remodeling in patients with COVID-19 [12]. However, its relationship with echocardiographic parameters across HF phenotypes during acute disease and the post-acute period remains insufficiently explored [13].

The aim of this study was to examine associations between Gal-3 levels and echocardiographic parameters across acute COVID-19 heart failure phenotypes and in a separate post-acute comparator cohort.

METHODS

Study design and setting

This single-center retrospective observational study was conducted at the First University Clinic of Tbilisi State Medical University, Tbilisi, Georgia, using clinical records from September 2022 to September 2023. The study used existing clinical, laboratory, and echocardiographic records and involved no prospectively assigned intervention. Reporting was guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Study population and sampling

The study records included 86 participants: 61 adults evaluated during hospitalization for acute COVID-19 and a separate cohort of 25 adults evaluated approximately 2 months after infection. Acute-phase assessments were obtained within 24 hours after admission and during the index hospitalization. Participants were selected retrospectively from eligible records using a non-probability sampling approach. No a priori sample size calculation was performed; the sample size reflected the eligible re-

cords available during the study period. Because sampling was not random and the analytical groups were markedly unequal in size, all analyses were considered exploratory.

Eligibility criteria

The inclusion criteria were age 18 years or older and laboratory confirmation of SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) using a nasopharyngeal or oropharyngeal swab. Acute-phase participants were hospitalized for COVID-19, whereas the post-acute comparator cohort attended an assessment approximately 2 months after infection. The exclusion criteria were age younger than 18 years, an inadequate echocardiographic window, type 1 or type 2 diabetes mellitus except steroid-induced hyperglycemia, mechanical ventilation, pregnancy, dialysis, and type 4 or type 5 myocardial infarction, defined as procedure-related myocardial infarction or myocardial injury.

Analytical group classification

The 61 acute-phase participants were classified according to the left ventricular ejection fraction (LVEF) thresholds in the 2022 AHA/ACC/HFSA heart failure guideline [14]. Group 1 comprised 6 participants with heart failure with reduced ejection fraction (HFrEF; LVEF $\leq$ 40%). Group 2 comprised 20 participants with heart failure with mildly reduced ejection fraction (HFmrEF; LVEF 41%-49%) and evidence of increased left ventricular filling pressures. Group 3 comprised 35 participants with heart failure with preserved ejection fraction (HFpEF; LVEF $\geq$ 50%) and evidence of increased left ventricular filling pressures. Group 4 comprised 25 participants evaluated approximately 2 months after COVID-19 and served as a post-acute comparator; it was not considered a fourth guideline-defined heart failure phenotype or a cohort with formally diagnosed post-COVID-19 syndrome.

Heart failure status and New York Heart Association functional class were abstracted from the clinical records. For HFmrEF and HFpEF, increased filling pressures were identified based on the available clinical and echocardiographic evidence.

Timing of clinical and laboratory assessment

For the acute-phase groups, clinical and laboratory assessment was performed at admission, and transthoracic echocardiography was performed during the index hospitalization. Serum galectin-3 was measured from the admission sample. For the post-acute comparator, galectin-3 measurement and echocardiographic assessment were performed at the approximately 2-month visit.

Echocardiographic assessment

Transthoracic echocardiography was performed using a GE Healthcare Vivid S5 cardiovascular ultrasound system.

Standard linear measurements, M-mode, two-dimensional imaging, and Doppler techniques were used. The recorded variables were LVEF (%), fractional shortening (%), E/e' ratio, left ventricular mass (g), left ventricular end-diastolic volume (mL), left ventricular end-systolic volume (mL), posterior wall thickness (cm), interventricular septal thickness in diastole (cm), left ventricular end-diastolic diameter (cm), left atrial diameter (cm), left atrial volume (mL), left atrial volume index (mL/m²), right ventricular diameter (cm), pulmonary artery systolic pressure (mmHg), tricuspid annular plane systolic excursion (mm), right ventricular fractional area change (%), and maximum tricuspid regurgitation velocity (m/s). Measurements were interpreted with reference to the American Society of Echocardiography/European Association of Cardiovascular Imaging chamber-quantification recommendations [15]. LVEF and chamber measurements were abstracted from the clinical echocardiography reports.

Galectin-3 measurement

Serum galectin-3 was measured using a commercially available human galectin-3 enzyme-linked immunosorbent assay (ELISA) kit manufactured by SUNLONG Biotech. Samples from the acute-phase groups were obtained at hospital admission, whereas samples from the post-acute comparator were obtained at the approximately 2-month assessment.

Study outcomes

The principal analytical objective was to examine associations between serum galectin-3 and recorded echocardiographic parameters within each analytical group. Secondary analyses compared galectin-3 and echocardiographic measurements across the three acute heart failure groups and the post-acute comparator. No single echocardiographic variable was documented as a pre-specified primary outcome; therefore, the correlation analyses were treated as exploratory.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation, and categorical variables as counts and percentages. During revision, between-group comparisons

were recalculated from the reported group sample sizes, means, and standard deviations using Welch's one-way analysis of variance. When an omnibus test was statistically significant, Games-Howell post hoc *p*-values were calculated from the same summary statistics.

Associations between galectin-3 and echocardiographic variables were summarized using the reported Spearman rank correlation coefficient (*rho*). Two-sided *p*-values were calculated from the reported *rho* value and the subgroup sample sizes using the *t*-approximation. A nominal *p*<0.05 threshold was used; values below 0.001 were reported as *p*<0.001. No multiplicity adjustment was applied, and all correlation findings were interpreted as exploratory.

No imputation was performed. Because of the modest sample size, marked subgroup imbalance, and the number of potential confounders, no multivariable model was reported; the analyses were limited to descriptive and unadjusted exploratory associations.

Ethics

The study protocol was reviewed and approved by the Tbilisi State Medical University Research Ethics Committee (Meeting No. 4, Approval No. 2022/97; review period: July 22, 2022-August 2, 2022). The requirement for informed consent was waived because of the retrospective design. Patient information was analyzed in de-identified form, and the study was conducted in accordance with the Declaration of Helsinki.

RESULTS

Study population and baseline characteristics

The present study included 86 participants, of whom 61 were evaluated during hospitalization for acute COVID-19 and 25 were evaluated approximately 2 months after infection. The acute-phase cohort comprised 6 participants with HFrEF, 20 with HFmrEF, and 35 with HFpEF. The post-acute cohort was analyzed as a separate comparator and not as a fourth guideline-defined heart failure phenotype. Group distribution, sex, and baseline characteristics are summarized in Table 1.

Age and BMI did not differ significantly among groups (*p*=0.285 and *p*=0.308, respectively).

Table 1. Distribution and baseline characteristics of the analytical groups

Characteristic	HFrEF (n=6)	HFmrEF (n=20)	HFpEF (n=35)	Comparator (n=25)	Overall <i>p</i> value
LVEF classification	<=40%	41-49%	>=50%	Separate comparator	-
Participants, n (% of total)	6 (7.0)	20 (23.3)	35 (40.7)	25 (29.1)	-
Male, n (%)	3 (50.0)	12 (60.0)	18 (51.4)	11 (44.0)	-
Female, n (%)	3 (50.0)	8 (40.0)	17 (48.6)	14 (56.0)	-
Age, years	76.8 ± 10.5	69.3 ± 6.6	73.2 ± 12.4	71.8 ± 16.8	0.285
BMI, kg/m ²	31.3 ± 7.9	27.3 ± 6.5	26.1 ± 3.1	25.4 ± 3.8	0.308

Values are shown as n (%) or mean ± SD. Overall *p*-values are from Welch one-way analysis of variance. The post-COVID-19 group was a separate comparator rather than a guideline-defined heart failure phenotype. The comparator cohort consisted of participants assessed approximately 2 months after COVID-19 infection. Abbreviations: BMI- body mass index, HFrEF- heart failure with reduced ejection fraction, HFmrEF- heart failure with mildly reduced ejection fraction, HFpEF- heart failure with preserved ejection fraction, LVEF- left ventricular ejection fraction.

Galectin-3 and echocardiographic comparisons

Mean galectin-3 levels were 19.4 ± 5.3 ng/mL in HFrEF, 16.8 ± 7.1 ng/mL in HFmrEF, 10.5 ± 7.7 ng/mL in HFpEF, and 8.5 ± 5.9 ng/mL in the post-acute comparator. Galectin-3 differed among groups (Welch $p < 0.001$). Games-Howell comparisons were significant for HFrEF versus HFpEF ($p = 0.027$), HFrEF versus the post-acute comparator ($p = 0.009$), HFmrEF versus HFpEF ($p = 0.019$), and HFmrEF versus the post-acute comparator ($p < 0.001$), but not for HFrEF versus HFmrEF or HFpEF versus the post-acute comparator (Table 2).

LVEF and fractional shortening differed among groups (both $p < 0.001$), as expected from the LVEF-based phenotype definitions. E/e' ratio, interventricular septal thickness, posterior wall thickness, LVEDV, LVESV, left atrial volume, and LAVI also differed in the omnibus analyses. In Games-Howell post hoc comparisons, the most consistent structural differences involved greater systolic impairment and LVESV in HFrEF, greater wall thickness in HFmrEF, and larger atrial measures in HFmrEF than in HFpEF and the post-acute comparator (Table 2).

Right ventricular diameter did not differ significantly among groups. TAPSE, RVFAC, PASP, and TR Vmax differed in omnibus analyses; Games-Howell pairwise differences were observed for TAPSE and RVFAC between HFmrEF and the post-acute comparator and for PASP between HFrEF and both HFpEF and the post-acute comparator. No Games-Howell pairwise comparison was significant for TR Vmax (Table 2).

Group-stratified correlations

The complete group-stratified Spearman correlations are presented in Table 3. In HFrEF ($n = 6$), galectin-3 correlated inversely with LVEF ($\rho = -0.957$, $p = 0.003$) and fractional shortening ($\rho = -0.946$, $p = 0.004$) and positively with LVESV ($\rho = 0.895$, $p = 0.016$). Because this subgroup contained only six participants, these estimates were considered unstable.

In HFmrEF, galectin-3 correlated with interventricular septal thickness ($\rho = 0.460$, $p = 0.041$) and LAVI ($\rho = 0.462$, $p = 0.040$). In HFpEF, galectin-3 correlated inversely with LVEF ($\rho = -0.413$, $p = 0.014$) and positively with left atrial volume ($\rho = 0.538$, $p < 0.001$) and LAVI ($\rho = 0.532$, $p = 0.001$).

Table 2. Galectin-3 and echocardiographic measurements across analytical groups

Parameter	HFrEF (n=6)	HFmrEF (n=20)	HFpEF (n=35)	Post-acute comparator (n=25)	Welch p	Significant Games-Howell comparisons
Gal-3, ng/mL	19.4 ± 5.3	16.8 ± 7.1	10.5 ± 7.7	8.5 ± 5.9	<0.001	G1-G3 0.027; G1-G4 0.009; G2-G3 0.019; G2-G4 <0.001
LVEF, %	31.3 ± 8.1	45.9 ± 2.0	55.1 ± 3.6	53.2 ± 6.9	<0.001	G1-G2 0.024; G1-G3 0.003; G1-G4 0.002; G2-G3 <0.001; G2-G4 <0.001
FS, %	15.8 ± 4.0	23.2 ± 1.0	27.5 ± 2.0	26.8 ± 3.4	<0.001	G1-G2 0.022; G1-G3 0.003; G1-G4 0.002; G2-G3 <0.001; G2-G4 <0.001
E/e' ratio	16.2 ± 4.8	10.7 ± 2.6	8.6 ± 2.0	8.3 ± 2.7	0.001	G1-G3 0.039; G1-G4 0.032; G2-G3 0.023; G2-G4 0.027
IVST, cm	1.200 ± 0.063	1.365 ± 0.124	1.289 ± 0.176	1.228 ± 0.215	0.002	G1-G2 0.002
PWT, cm	1.100 ± 0.063	1.250 ± 0.097	1.163 ± 0.144	1.136 ± 0.158	0.001	G1-G2 0.003; G2-G3 0.048; G2-G4 0.024
LVEDV, mL	174.0 ± 46.8	121.5 ± 19.4	112.3 ± 13.3	114.9 ± 20.4	0.021	None
LVESV, mL	123.0 ± 41.8	66.2 ± 11.5	50.9 ± 9.1	54.9 ± 18.8	<0.001	G1-G3 0.030; G1-G4 0.035; G2-G3 <0.001
LA volume, mL	48.6 ± 31.8	44.1 ± 15.7	31.6 ± 10.1	30.0 ± 11.2	0.017	G2-G3 0.017; G2-G4 0.009
LAVI, mL/m ²	26.1 ± 10.3	22.9 ± 8.6	17.0 ± 5.5	16.4 ± 6.6	0.024	G2-G3 0.050; G2-G4 0.044
RV diameter, cm	3.717 ± 0.293	3.480 ± 0.098	3.406 ± 0.380	3.388 ± 0.285	0.103	None
TAPSE, mm	19.2 ± 2.6	20.1 ± 0.9	21.0 ± 2.2	21.6 ± 1.6	0.006	G2-G4 0.002
RVFAC, %	44.3 ± 8.2	44.7 ± 3.0	46.7 ± 5.4	48.3 ± 3.2	0.010	G2-G4 0.002
PASP, mmHg	55.6 ± 13.6	43.0 ± 12.3	34.8 ± 10.2	34.6 ± 9.9	0.004	G1-G3 0.044; G1-G4 0.042
TR Vmax, m/s	3.233 ± 0.459	2.990 ± 0.458	2.663 ± 0.420	2.692 ± 0.414	0.016	None

Values are shown as mean $\pm$ SD. G1=HFrEF; G2=HFmrEF; G3=HFpEF; G4=post-acute comparator. Pairwise p -values are Games-Howell post hoc comparisons and are shown only when significant at the nominal 0.05 level. Right atrial diameter was not included following internal data-quality review. LVEF and FS comparisons partly reflect the LVEF-based definitions of the acute heart failure groups. Abbreviations: EF – ejection fraction, FS – fractional shortening. Gal-3 – galectin-3, HF – heart failure, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, IVST – interventricular septal thickness in diastole, LA – left atrium / left atrial volume, LAVI – left atrial volume index, LV – left ventricle / left ventricular, LVEDV – left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, LVESV – left ventricular end-systolic volume, PASP – pulmonary artery systolic pressure, PWT – posterior wall thickness, RV – right ventricle, RVFAC – right ventricular fractional area change, TAPSE – tricuspid annular plane systolic excursion, TR Vmax – maximum tricuspid regurgitation velocity

In the post-acute comparator, galectin-3 correlated with LVEF ($\rho=-0.501, p=0.011$), fractional shortening ($\rho=-0.487, p=0.014$), E/e' ($\rho=0.525, p=0.007$), LVEDV ($\rho=0.514, p=0.009$), LVESV ($\rho=0.535, p=0.006$), LV mass ($\rho=0.530, p=0.006$), left atrial volume ($\rho=0.437, p=0.029$), and LAVI ($\rho=0.403, p=0.046$). No significant group-stratified correlations were observed for TAPSE, RVFAC, PASP, or TR Vmax. No multiplicity adjustment was applied; all correlation findings were exploratory.

DISCUSSION

This exploratory study found that galectin-3 differed across the four analytical groups and was associated with selected echocardiographic measurements within several groups. The strongest observed group-stratified associations involved systolic indices and LVESV in HFrEF, atrial measures in HFpEF, and systolic, diastolic, ventricular, and atrial measures in the post-acute comparator. These findings require cautious interpretation because the analyses were cross-sectional, the groups were small and uneven, and multiple correlations were examined without multiplicity adjustment.

The higher mean galectin-3 values in HFrEF and HFmrEF than in HFpEF and the post-acute comparator are directionally consistent with the proposed relationship of galectin-3 to inflammation and fibrotic remodeling in heart failure and COVID-19 [1,2,12,17]. However, the absence of significant Games-Howell pairwise differences between HFrEF and HFmrEF and between HFpEF and the post-acute comparator indicates that the data do not support a simple graded relationship across all groups.

In HFrEF, the inverse correlations with LVEF and fractional shortening and the positive correlation with LVESV

are compatible with an association between higher galectin-3 and more impaired systolic function. Nevertheless, this subgroup contained only six participants. Correlation estimates from such a small group are highly sensitive to individual observations and should be regarded as hypothesis-generating rather than as evidence of a stable HFrEF-specific relationship.

In HFmrEF, associations with interventricular septal thickness and LAVI may reflect structural and atrial remodeling. In HFpEF, the associations with left atrial volume and LAVI are compatible with chronic filling-pressure burden and atrial remodeling, central features of HFpEF pathophysiology [8,13,14]. These interpretations remain tentative because formal interaction testing was not performed and the analyses did not establish that the strength of association differed between phenotypes.

In the post-acute comparator, galectin-3 was associated with LVEF, fractional shortening, E/e' , ventricular volumes, LV mass, and atrial measures. This pattern may be compatible with persistent structural and functional abnormalities after infection [9-11,16]. It cannot, however, be interpreted as evidence that COVID-19 caused ongoing remodeling or that galectin-3 predicts subsequent outcomes. The post-acute participants were biologically distinct from the hospitalized acute-phase groups, and the analyses did not account for pre-existing cardiovascular disease, renal function, acute disease severity, or treatment exposure.

Several between-group echocardiographic differences require contextual interpretation. Differences in LVEF and fractional shortening were expected because the acute groups were defined using LVEF thresholds; these findings therefore do not independently validate biological differences among phenotypes. The remaining differ-

Table 3. Exploratory correlations between galectin-3 and echocardiographic measurements

Parameter	HFrEF (n=6)	HFmrEF (n=20)	HFpEF (n=35)	Post-acute comparator (n=25)
LVEF	-0.957 (0.003)*	0.298 (0.202)	-0.413 (0.014)*	-0.501 (0.011)*
FS	-0.946 (0.004)*	0.309 (0.185)	-0.299 (0.081)	-0.487 (0.014)*
E/e' ratio	0.527 (0.283)	-0.132 (0.579)	0.217 (0.211)	0.525 (0.007)*
IVST	-0.611 (0.198)	0.460 (0.041)*	0.206 (0.235)	0.118 (0.574)
PWT	-0.611 (0.198)	0.343 (0.139)	0.255 (0.139)	0.114 (0.587)
LVEDD	0.674 (0.142)	-0.093 (0.697)	0.268 (0.120)	0.383 (0.059)
LVEDV	0.754 (0.083)	-0.119 (0.617)	0.160 (0.359)	0.514 (0.009)*
LVESV	0.895 (0.016)*	0.185 (0.435)	0.278 (0.106)	0.535 (0.006)*
LV mass	0.785 (0.064)	0.020 (0.933)	0.203 (0.242)	0.530 (0.006)*
LA volume	0.615 (0.194)	0.414 (0.070)	0.538 (<0.001)*	0.437 (0.029)*
LAVI	0.658 (0.155)	0.462 (0.040)*	0.532 (0.001)*	0.403 (0.046)*
TAPSE	-0.567 (0.241)	0.396 (0.084)	-0.262 (0.128)	-0.241 (0.246)
RVFAC	-0.526 (0.284)	-0.237 (0.314)	-0.291 (0.090)	-0.153 (0.465)
PASP	0.499 (0.314)	0.099 (0.678)	0.142 (0.416)	0.357 (0.080)
TR Vmax	0.311 (0.549)	0.015 (0.950)	0.034 (0.846)	0.313 (0.128)

Values are shown as Spearman rho (two-sided p-value). * $p<0.05$. No multiplicity adjustment was applied; all correlations are exploratory. Correlation coefficients in HFrEF should be interpreted with particular caution because n=6. Right atrial diameter was not included following internal data-quality review. Abbreviations: EF – ejection fraction, FS – fractional shortening. HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, IVST – interventricular septal thickness in diastole, LA – left atrium / left atrial volume, LAVI – left atrial volume index, LV – left ventricle / left ventricular, LVEDD – left ventricular end-diastolic diameter, LVEDV – left ventricular end-diastolic volume, LVEF – left ventricular ejection fraction, LVESV – left ventricular end-systolic volume, PASP – pulmonary artery systolic pressure, PWT – posterior wall thickness, RV – right ventricle, RVFAC – right ventricular fractional area change, TAPSE – tricuspid annular plane systolic excursion, TR Vmax – maximum tricuspid regurgitation velocity

ences in wall thickness, chamber volumes, atrial measures, and selected right-heart variables may describe the sample but cannot be attributed to galectin-3 or COVID-19 phase without adjusted longitudinal analyses.

The present results do not establish causality, an independent biomarker effect, prognostic value, or clinical usefulness for risk stratification. Larger prospective studies should prespecify primary echocardiographic outcomes, recruit adequately sized and balanced phenotype groups, document assay and imaging methods prospectively, adjust for renal and cardiovascular confounders, and include longitudinal clinical outcomes.

Limitations

The overall sample was modest and the groups were markedly uneven, particularly HFrEF (n=6), resulting in limited power and unstable subgroup correlations. The single-center retrospective design and non-probability sampling increased the potential for selection bias, limited generalizability, and precluded causal inference. The large number of exploratory correlations increased the risk of false-positive findings, and no multiplicity adjustment was applied. The acute-phase and post-acute cohorts were biologically distinct, and the analyses did not adjust for renal function, baseline cardiovascular status, disease severity, or treatment exposure. The exact LVEF calculation technique, operator reproducibility procedures, detailed galectin-3 preanalytical and assay-performance characteristics, and the individual interval between blood collection and echocardiography were not fully documented. Right atrial diameter was excluded because its reported summary was internally inconsistent. Variable-specific missingness was not reported. Finally, the post-acute cohort was assessed only once, approximately 2 months after infection, without pre-infection measurements or longer-term outcomes.

CONCLUSIONS

Galectin-3 differed across the four analytical groups and was associated with selected echocardiographic measures in acute COVID-19 heart failure phenotypes and the post-acute comparator. Group-stratified associations involved systolic, ventricular, diastolic, and atrial measurements, but their pattern was not uniform.

The findings are exploratory. The very small HFrEF subgroup, unequal group sizes, multiple unadjusted correlation tests, absence of a robust multivariable model, and cross-sectional design prevent conclusions about independent associations, causality, prognosis, or clinical utility.

Confirmation requires larger prospective studies with balanced groups, prespecified outcomes, complete laboratory and echocardiographic documentation, multivariable adjustment, and longitudinal follow-up.

ABBREVIATIONS

BMI – body mass index
 COVID-19 – coronavirus disease 2019
 EF – ejection fraction
 ELISA – enzyme-linked immunosorbent assay
 FS – fractional shortening
 Gal-3 – galectin-3
 HF – heart failure
 HFmrEF – heart failure with mildly reduced ejection fraction
 HFrEF – heart failure with reduced ejection fraction
 IVST – interventricular septal thickness in diastole
 LA – left atrium / left atrial volume
 LAd – left atrial diameter
 LAVI – left atrial volume index
 LV – left ventricle / left ventricular
 LVEDD – left ventricular end-diastolic diameter
 LVEDV – left ventricular end-diastolic volume
 LVEF – left ventricular ejection fraction
 LVESV – left ventricular end-systolic volume
 NYHA – New York Heart Association
 PASC – post-acute sequelae of SARS-CoV-2 infection
 PASP – pulmonary artery systolic pressure
 PWT – posterior wall thickness
 RT-PCR – reverse transcription polymerase chain reaction
 RV – right ventricle
 RVd – right ventricular diameter
 RVFAC – right ventricular fractional area change
 SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
 TAPSE – tricuspid annular plane systolic excursion
 TR Vmax – maximum tricuspid regurgitation velocity
 TTE – transthoracic echocardiography

ACKNOWLEDGEMENT

None.

AUTHORS' CONTRIBUTION

NE – investigation, data curation, validation, writing (original draft)
 NK – supervision, project administration, writing (review & editing)
 KK – supervision, project administration, resources
 NG – methodology, formal analysis, validation
 DK – data acquisition, data interpretation, writing (original draft), writing (review & editing)
 LR – study design, data acquisition, literature review, writing (original draft), writing (review & editing)
 All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None to declare.

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