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Assessment of novel cardiovascular biomarkers in chronic obstructive pulmonary disease

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Abstract

Background Cardiovascular disease is a common comorbidity in chronic obstructive pulmonary disease (COPD) and pre-COPD patients, contributing significantly to morbidity and mortality. We aimed to investigate whether Galectin-3 (Gal-3) levels correlate with cardiovascular biomarkers and cardiopulmonary function in COPD and pre-COPD patients to assess its potential role as a marker for cardiovascular comorbidity.

Methods Community-dwelling adults with and without COPD were recruited. Biomarkers including Gal-3, high-sensitivity cardiac troponin T (hs-cTnT), and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured. Subjects underwent pulmonary function tests, chest CT, echocardiograms, and a 6-minute walking test. The relationships between biomarkers and cardiopulmonary function were examined.

Results Among 120 subjects (97 COPD, 23 pre-COPD), the mean age was 70.2 years, and the mean predicted forced expiratory volume in 1 s (FEV1%) was 68.5%. Gal-3 levels averaged 1733.7 pg/mL. Gal-3 significantly correlated with NT-proBNP ($\rho = 0.229$, $p = 0.012$) and negatively with maximal pulse rate during the 6-minute walking test (ρ=-0.185, $p = 0.043$). No significant correlation was found between Gal-3 and hs-cTnT levels. However, hs-cTnT levels showed significant negative correlations with age (ρ=-0.526, $p < 0.001$), FEV1% (ρ=-0.373, $p < 0.001$), E/A ratio (ρ=-0.390, $p < 0.001$), and walking distance (ρ=-0.444, $p < 0.001$), and positive correlations with deceleration time ($\rho = 0.299$, $p = 0.001$), right ventricular systolic pressure ($\rho = 0.197$, $p = 0.037$), and high-sensitivity C-reactive protein ($\rho = 0.212$, $p = 0.020$).

Conclusions Gal-3 levels show correlations with NT-proBNP and maximal pulse rate, supporting its investigation as a potential marker for cardiovascular comorbidity in COPD and pre-COPD populations.

Keywords COPD, Cardiovascular biomarker, Cardiovascular comorbidity, Galectin-3, High-sensitivity cardiac troponin T

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Introduction

Approximately 30% of chronic obstructive pulmonary disease (COPD)-related deaths are due to cardiovascular disease [1]. The risk of cardiovascular diseases, including ischemic heart disease, cardiac dysrhythmia, heart failure, and diseases of the arteries, is higher in individuals with COPD compared to healthy subjects [2]. Common risk factors such as aging and smoking contribute to this higher comorbidity. It is crucial to understand the mechanisms linking cardiovascular disease and COPD to develop effective treatment and management strategies, particularly in primary care settings [3, 4].

N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were found to be significantly elevated in acute exacerbation of COPD, pulmonary hypertension, and chronic heart failure [5]. However, in clinical practice, it can be challenging to determine if a patient's worsening condition is due to respiratory issues or cardiovascular comorbidity. Comprehensive evaluations of COPD and comorbidities, including markers for lung fibrosis (KL-6 and SP-D), echocardiography, and the 6-minute walking test (6MWT), are essential for determining treatment strategies and prognosis [6].

A previous report confirmed that high-sensitivity troponin levels in stable COPD patients were correlated with high-sensitivity CRP levels, age, and estimated right ventricular pressure, suggesting COPD disease activity [7]. Persistent systemic chronic inflammation could induce subclinical myocardial injury even in stable COPD patients.

Myocardial fibrosis and remodelling are key mechanisms of cardiovascular disease progression [8, 9]. Galectin-3 (Gal-3) is a β-galactoside-binding lectin involved in various biological processes, including inflammation, fibrosis, and myocardial remodelling. Gal-3 contributes to myocardial fibrosis by promoting fibroblast activation and collagen deposition, which leads to the stiffening and scarring of myocardial tissue. This process is mediated through Gal-3's interaction with key signalling pathways such as the TGF-β/Smad pathway, which is known to induce extracellular matrix production [10]. Additionally, Gal-3 can enhance the inflammatory response by recruiting and activating macrophages, further contributing to tissue fibrosis and remodelling [11]. These mechanisms suggest that elevated Gal-3 levels may reflect ongoing myocardial fibrosis and remodelling in COPD patients with cardiovascular comorbidities [12].

Increased Gal-3 expression and neutrophil infiltration in severe COPD patients suggest a link between airway inflammation and Gal-3 expression [13, 14]. Elevated serum Gal-3 levels have been identified as potential biomarkers for COPD exacerbation [15]. Gal-3 may also play a crucial role in lysophagy as evidenced by a negative correlation between Gal-3 and tripartite motif 16 (TRIM16) in bronchial epithelial cells from COPD patients [16].

We hypothesized that Gal-3, elevated by chronic airway inflammation, might be involved in COPD pathogenesis and contribute to myocardial fibrosis and remodelling, thus impacting cardiovascular disease development in COPD patients. To test this hypothesis, we examined the relationship between Gal-3 and cardiopulmonary function, myocardial fibrosis and remodelling, and biomarkers related to aging and hs-cTnT in COPD patients.

Patients and methods

Participants

Subjects were recruited from the Respiratory Care Clinic of Nippon Medical School between December 2016 and November 30, 2022. Recruitment occurred prior to the COVID-19 pandemic; however, some follow-up visits were minimally impacted by pandemic-related restrictions. Community-dwelling adults, with and without a formal diagnosis of COPD, who had a smoking history and symptoms of dyspnoea during exertion, prolonged coughing, and/or sputum production were included. A diagnosis of COPD was defined as a history of long-term exposure to tobacco smoke and other toxic substances and a post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio of less than 0.70, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [17]. Pre-COPD subjects were identified as those having similar symptoms and exposure to hazardous substances as COPD patients but did not meet the diagnostic criteria for COPD.

Individuals undergoing treatment or presenting with any of the following pulmonary and cardiovascular diseases were excluded: bronchiectasis, interstitial pneumonia, ischemic heart disease, any type of arrhythmia, and congestive heart failure. A total of 120 stable subjects, with or without cardiovascular comorbidities, were enrolled in the present study.

All methods in this study were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice. This prospective study was approved by the ethics committee of Nippon Medical School (approval number: 28−16), and all patients provided written informed consent before enrolment. Patient confidentiality was strictly maintained by anonymizing all data before analysis, ensuring that no identifiable information was accessible during the study.

Outcome measurements

All subjects underwent chest roentgenography from both directions, electrocardiogram (ECG), routine blood

chemistry, pulmonary function tests (PFTs), high-resolution chest computed tomography (HRCT), echocardiogram, and the 6-minute walk test (6MWT).

ECG was performed using a diagnostic ultrasound system (Aplio SSA-770 A; Toshiba Medical Systems Co., Japan) to identify obvious heart diseases such as arrhythmia and previous myocardial infarction.

PFTs were performed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [18], using specialized lung function testing equipment with computer processing (Chestac 55; Chest Co., Japan).

HRCT parameters, including the percentage of low attenuation area (LAA%) for the upper, middle, and lower bilateral lung fields and the overall mean values, were calculated as previously reported [7].

The 6MWT was conducted according to ATS/ERS standards [19], during which oximetry was measured every 5 s with a pulse oximeter (PULSEOX; TEIJIN Co., Tokyo, Japan). A qualified respiratory specialist supervised all tests.

Serum biomarker measurements

Serum samples were collected and preserved at -80 °C for biomarker measurements. Gal-3, hs-cTnT, NT-proBNP, high-sensitivity C-reactive protein (hs-CRP), interleukin 6 (IL-6), surfactant protein D (SP-D), club cell protein 16 (CC16), and soluble receptor for advanced glycation end products (sRAGE) were measured using an electrochemiluminescence immunoassay kit (SRL, Inc., Tokyo, Japan). The lower limit of detection for Gal-3 and hs-cTnT were 117.19 pg/mL and 0.003 ng/mL, respectively, with a cut-off value of 0.1 ng/mL for hs-cTnT.

Statistical analysis

Gal-3 and hs-cTnT concentrations were not evenly distributed and were therefore logarithmically transformed. The associations between Gal-3 and hs-cTnT levels and other parameters were tested using Spearman's correlation analyses. Comparisons between COPD and pre-COPD subjects for Gal-3 and hs-cTnT levels were analysed using the Mann-Whitney U test. Furthermore, the associations between hs-cTnT levels and other parameters were tested using Spearman's correlation analyses and multivariate stepwise backward analyses. Data were analyzed using SPSS Statistics Version 23 (IBM Corporation, Armonk, NY, USA). All *p*-values were two-tailed, and a *p*-value of <0.05 was considered statistically significant.

Results

A total of 120 subjects with stable COPD or identified as pre-COPD were selected for this study. Table 1 displays the patients' characteristics. The mean age was 70.2 years, and there were 20 females. The mean FEV1% predicted for all subjects was 68.5%. Based on GOLD criteria, 97 subjects were diagnosed with COPD (stage I: 24, stage II: 41, stage III: 28, stage IV: 4), while 23 subjects were classified as pre-COPD. The mean hs-CRP, hs-TnT serum levels, and NT-proBNP serum levels were 1588.0 ng/mL, 0.012 ng/mL, and 109.2 pg/mL, respectively.

Results of HRCT, ECG, 6MWT, and blood tests are shown in Table 2. The mean LAA% for the upper lung

Table 1 Patient characteristics

	Subjects (*n* = 120)	Pre-COPD (*n* = 23)	COPD (*n* = 97)	*p*-value
Age (years)	70.2 ± 9.3	65.2 ± 11.2	71.4 ± 8.4	**0.0231**
Sex (male/female)	100/20	13/10	87/10	
BMI	22.8 ± 3.4	23.1 ± 4.1	23.0 ± 3.0	0.9065
COPD severity (Stages I/II/III/IV)			24/41/28/4	
Pulmonary function test				
FVC (L)	3.29 ± 0.82	3.33 ± 0.87	3.28 ± 0.81	0.7692
FEV1% (%)	55.8 ± 15.8	75.4 ± 5.8	51.2 ± 13.7	**< 0.0001**
FEV1%predicted (%)	68.5 ± 24.1	96.6 ± 16.2	61.8 ± 20.7	**< 0.0001**
IC (L)	2.33 ± 0.60	2.23 ± 0.51	2.35 ± 0.62	0.4943
%DLco/VA (%)	82.1 ± 26.3	102.0 ± 27.8	77.4 ± 23.7	**0.0006**
Blood test				
hs-CRP (ng/mL)	1588.0 ± 2991.1	2016.6 ± 3585.4	1486.3 ± 2844.3	0.7288
hs-TnT (ng/mL)	0.012 ± 0.021	0.007 ± 0.006	0.013 ± 0.023	**0.0008**
NT-proBNP (pg/mL)	109.2 ± 260.4	59.4 ± 56.2	120.9 ± 287.4	0.1498
SP-D (pg/mL)	64.5 ± 51.6	65.2 ± 51.8	64.3 ± 51.8	0.8702

Data are presented as mean ± SD or number. Boldface indicates a *P* value with statistical significance. BMI; body mass index, FVC; forced vital capacity, FEV1%; forced expiratory volume in 1 s, IC; inspiratory capacity, %DLco/VA; percent diffusing capacity of the lung for carbon monoxide/alveolar volume, hs-CRP; high-sensitivity C-reactive protein, hs-TnT; high-sensitivity cardiac troponin T, NT-proBNP; N-terminal pro-brain natriuretic peptide, SP-D; surfactant protein D

Table 2 Results of HRCT, echocardiography, 6-minute walking test, and blood tests

	Subjects (*n* = 120)	Pre-COPD (*n* = 23)	COPD (*n* = 97)	*p*-value
Chest HRCT				
LAA% for the upper lung field (%)	12.3 ± 17.5	2.2 ± 7.9	14.8 ± 18.3	**< 0.0001**
Echocardiography				
LVDd (mm)	46.8 ± 4.5	47.6 ± 3.8	46.2 ± 5.7	0.4452
EF (%)	67.5 ± 5.3	68.0 ± 4.0	68.5 ± 5.4	0.5705
E/A	0.80 ± 0.26	1.0 ± 0.3	0.85 ± 0.19	**0.0044**
DT (second)	223.8 ± 36.3	219.5 ± 39.3	208.1 ± 25.7	0.6202
E/E'	8.9 ± 2.1	9.3 ± 1.8	8.2 ± 1.6	0.2055
RVSP (mmHg)	27.3 ± 6.7	27.7 ± 4.6	24.7 ± 3.4	0.9470
CO (L/minute)	4.8 ± 0.9	4.7 ± 0.9	4.5 ± 1.3	0.7288
Six-minute walking test				
Walking distance (m)	527.5 ± 101.7	558.6 ± 86.4	520.1 ± 104.0	0.1066
Borg scale	3.4 ± 1.9	2.7 ± 1.8	3.6 ± 1.9	**0.0450**
Initiate SpO2 (%)	96.5 ± 1.4	97.1 ± 1.1	96.4 ± 1.4	**0.0235**
Minimal SpO2 (%)	91.0 ± 5.5	93.7 ± 3.3	90.3 ± 5.8	**0.0026**
Initiate PR (beats/minute)	77.1 ± 11.5	75.0 ± 10.0	77.6 ± 11.8	0.2996
Maximal PR (beats/minute)	124.0 ± 15.9	126.7 ± 11.7	123.3 ± 16.7	0.2526
Blood test				
Gal-3 (pg/mL)	1733.7 ± 4286.3	724.5 ± 780.9	1973.0 ± 4725.8	0.0565
IL-6 (pg/mL)	2.45 ± 4.41	3.83 ± 9.63	2.12 ± 1.50	0.2297
CC16 (ng/mL)	9.29 ± 5.69	8.95 ± 3.88	9.38 ± 6.05	0.5462
sRAGE (pg/mL)	1035.2 ± 554.6	1278.3 ± 721.5	977.6 ± 494.5	**0.0500**

Data are presented as mean ± SD or number. Boldface indicates a *P* value with statistical significance. HRCT; high resolution computer tomography, LAA; percentage of low attenuation area, LVDd; left ventricular end-diastolic dimension, EF; ejection fraction, E/A; early diastolic filling velocity/atrial filling velocity ratio, DT; deceleration time, E/E'; early diastolic filling velocity/early diastolic mitral annular velocity, RVSP; right ventricular systolic pressure, CO; cardiac output, SpO2; oxygen saturation, PR; pulse rate, IL-6; interleukin 6, CC16; club cell protein 16, sRAGE; soluble receptor for advanced glycation end products

field was 12.3% (COPD: 14.8%; pre-COPD: 2.2%). The mean right ventricular systolic pressure (RVSP) was 27.3 mmHg, and two subjects with COPD presented with pulmonary hypertension on echocardiogram. In the 6MWT, the mean walking distance and maximal pulse rate were 527.5 m and 124 beats per minute, respectively. The mean Gal-3 serum level was 1733.7 pg/mL.

The association between Gal-3 levels and demographic parameters is shown in Table 3. Gal-3 levels were significantly and positively correlated with NT-proBNP levels (ρ = 0.229, $p = 0.012$) and significantly and negatively correlated with maximal pulse rates during the 6-minute walking test (6MWT) (ρ=-0.185, $p = 0.043$) in the overall population. In the pre-COPD group, Gal-3 levels were significantly and positively correlated with NT-proBNP levels (ρ = 0.427, $p = 0.042$). In the COPD group, Gal-3 levels were significantly and positively correlated with NT-proBNP levels and significantly and negatively correlated with maximal pulse rates on the 6MWT (ρ = 0.206, $p = 0.049$; ρ=-0.211, $p = 0.049$, respectively).

A comparison between COPD and pre-COPD subjects for Gal-3 and hs-TnT levels is shown in Table 4, and the distribution of Gal-3 and hs-TnT by GOLD stages for pre-COPD and COPD is shown in Fig. 1. Since no differences were found for Gal-3 between the pre-COPD and COPD groups in Table 4, we examined whether significant differences were found for each GOLD stage (Fig. 1A). No significant group differences were found for Gal-3 in the Kruskal-Wallis test for each GOLD stage ($p = 0.2177$) (Fig. 1A). Conversely, a significant difference in hs-TnT levels was seen between COPD and pre-COPD subjects ($p = 0.001$), and significant group differences were observed in the Kruskal-Wallis test for each GOLD stage ($p = 0.0014$) (Fig. 1B).

The association between log hs-TnT levels and key cardiopulmonary parameters is shown in Table 5. In the overall population, log hs-TnT levels were significantly correlated with age, NT-proBNP, and IL-6 levels (ρ = 0.526, $p < 0.001$; ρ = 0.437, $p < 0.001$; ρ = 0.490, $p < 0.001$, respectively). Negative correlations were also observed with FEV1% predicted and walking distance (ρ=-0.388, $p < 0.001$; ρ=-0.444, $p < 0.001$, respectively). In the COPD group specifically, significant correlations were found with NT-proBNP and inflammatory markers, indicating hs-TnT's sensitivity in detecting changes in cardiopulmonary function.

Of the 120 patients, 6 with COPD had cardiovascular comorbidities (2 with secondary pulmonary hypertension, 1 with heart failure, 1 with paroxysmal tachycardia, 1 with aortic dissection, and 1 with Brugada-type ECG abnormality) during the study period. Stable Gal-3 levels of 662.8 ± 560.3 pg/mL were observed in these patients.

Table 3 Association between Galectin-3 and study parameters

	Subjects (*n* = 120)		Pre-COPD (*n* = 23)		COPD (*n* = 97)	
	ρ	*p*-value	*ρ*	*p*-value	*ρ*	*p*-value
Pulmonary function test						
FVC	-0.042	0.647	-0.155	0.480	-0.011	0.917
FEV1	-0.122	0.183	-0.236	0.279	-0.043	0.673
FEV1%predicted	-0.109	0.236	0.118	0.593	-0.043	0.653
IC	-0.063	0.497	-0.197	0.368	-0.056	0.589
%Dlco/VA	-0.109	0.236	-0.195	0.373	-0.029	0.781
Chest HRCT						
LAA% for the upper lung field	0.051	0.578	0.006	0.979	-0.012	0.906
Echocardiography						
LVDd	0.016	0.862	-0.046	0.834	0.055	0.599
EF	0.013	0.891	-0.243	0.264	0.067	0.522
E/A	-0.01	0.914	-0.060	0.787	0.054	0.608
DT	-0.094	0.314	-0.145	0.509	-0.09	0.391
E/E'	0.015	0.874	0.217	0.320	0.026	0.807
RVSP	-0.027	0.776	-0.207	0.369	0.014	0.896
CO	-0.137	0.142	0.096	0.664	-0.189	0.068
Six-minute walking test						
Walking distance	-0.11	0.231	-0.036	0.870	-0.091	0.373
Borg scale	-0.029	0.755	-0.149	0.497	-0.067	0.516
Initiate SpO2	0.109	0.238	0.365	0.087	0.106	0.302
Minimal SpO2	0.033	0.721	-0.171	0.436	0.106	0.302
Initiate PR	-0.038	0.679	-0.018	0.936	-0.067	0.514
Maximal PR	-0.185	**0.043**	-0.109	0.621	-0.211	**0.049**
Blood test						
hs-CRP	0.053	0.566	-0.032	0.887	0.041	0.694
hs-TnT	0.177	0.053	-0.032	0.887	0.163	0.111
NT-proBNP	0.229	**0.012**	0.427	**0.042**	0.206	**0.049**
SP-D	-0.012	0.899	0.110	0.618	-0.024	0.819
IL-6	0.074	0.421	0.231	0.290	0.038	0.712
CC16	0.078	0.396	-0.078	0.725	0.122	0.236
sRAGE	0.014	0.878	-0.070	0.750	0.054	0.601

Boldface indicates a *P* value with statistical significance. FVC; forced vital capacity, FEV1%; forced expiratory volume in 1 second, IC; inspiratory capacity, %DLco/VA; percent diffusing capacity of the lung for carbon monoxide/alveolar volume, HRCT; high-resolution computer tomography, LAA; percentage of low attenuation area, LVDd; left ventricular end-diastolic dimension, EF; ejection fraction, E/A; early diastolic filling velocity/atrial filling velocity ratio, DT; deceleration time, E/E'; early diastolic filling velocity/early diastolic mitral annular velocity, RVSP; right ventricular systolic pressure, CO; cardiac output, SpO2; oxygen saturation, PR; pulse rate, hs-CRP; high-sensitivity C-reactive protein, hs-TnT; high-sensitivity cardiac troponin T, NT-proBNP; N-terminal pro-brain natriuretic peptide, SP-D; surfactant protein D, IL-6; interleukin 6, CC16; club cell protein 16, sRAGE; soluble receptor for advanced glycation end products

Table 4 Comparison between COPD and pre-COPD subjects for Galectin-3 and hs-TnT levels

	COPD (*n* = 97)	Pre-COPD (*n* = 23)	*p*-value
Gal-3 (pg/mL)	1973.0 ± 4725.8	724.5 ± 780.9	0.057
hs-TnT (ng/mL)	0.013 ± 0.023	0.007 ± 0.006	**0.001**

Data are presented as mean ± SD or number. Boldface indicates a *P* value with statistical significance. COPD; chronic obstructive pulmonary disease, hs-TnT; high-sensitivity cardiac troponin T

Discussion

In this study, we found that Gal-3 levels significantly correlated with NT-proBNP levels and maximal pulse rates on the 6MWT in patients with both pre- and stable COPD. Furthermore, hs-TnT levels were significantly and negatively correlated with age, FEV1%, E/A, and 6MWT distance, and significantly and positively correlated with deceleration time (DT), RVSP, and hs-CRP. These findings suggest that hs-TnT may be a more sensitive biomarker of cardiopulmonary function changes than Gal-3, with significant differences observed between pre-COPD and COPD groups, as well as between COPD GOLD stages.

Heart failure is a major comorbidity and contributor to mortality in patients with COPD. While we considered Gal-3 as a potential marker for the early identification and prediction of cardiovascular diseases, including heart failure, in COPD, our findings did not confirm this hypothesis. Lagan et al. demonstrated [20] that COPD is significantly and independently associated with the extent of myocardial fibrosis as assessed by cardiac magnetic resonance (CMR) and is independently linked to

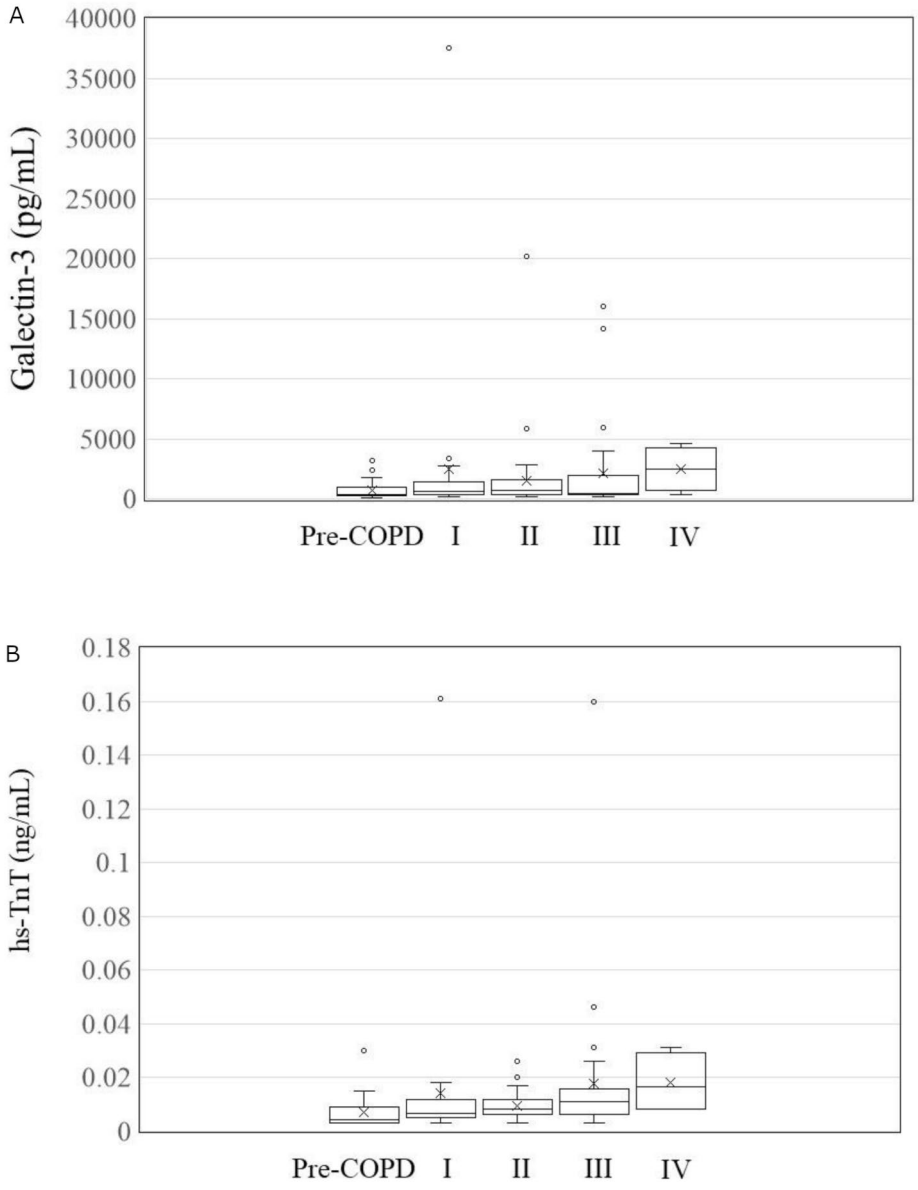

Fig. 1 (**A**) Galectin-3 (Gal-3) levels by GOLD stages. Pre-COPD indicates patients at risk for COPD but not yet diagnosed with the disease. GOLD stages I-IV represent increasing severity of COPD. (**B**) High-sensitivity cardiac troponin T (hs-TnT) levels by GOLD stages. Pre-COPD indicates patients at risk for COPD but not yet diagnosed with the disease. GOLD stages I-IV represent increasing severity of COPD

heart failure-related hospitalizations and all-cause mortality during a median follow-up period of 726 days. This finding supports the potential pathophysiological link between COPD and heart failure, aligning with our study's exploration of Gal-3's role in myocardial fibrosis and cardiovascular outcomes in COPD patients. While we have not confirmed myocardial fibrosis histologically in COPD patients, that study suggested that such a pathophysiology may exist, even though these findings remain speculative. This supports the rationale for further exploration of Gal-3's role in cardiovascular disease development within COPD populations, using more longitudinal designs that could capture the progression and effects over time.

Previous studies have noted correlations between Gal-3 and cardiac function parameters such as right ventricular dysfunction and subclinical vascular disease. Horodinschi et al. highlighted [21] the need for early detection of cardiovascular comorbidities in COPD while Wannamethee et al. further demonstrated [22] that the association of Gal-3 with subclinical vascular disease, reinforcing its potential for cardiovascular risk assessment. Furthermore, Zaborsca et al. found [23] that Gal-3 is related to right ventricular dysfunction in heart failure

Table 5 Association between log hs-TnT levels and study parameters in all subjects

	Subjects (*n* = 120)		Pre-COPD (*n* = 23)		COPD (*n* = 97)	
	ρ	*p*-value	ρ	*p*-value	ρ	*p*-value
Age	0.526	**< 0.001**	0.672	**< 0.001**	0.445	**< 0.001**
Pulmonary function test						
FVC	-0.223	0.015	-0.318	0.140	-0.199	0.051
FEV1	-0.388	**< 0.001**	-0.309	0.152	-0.326	**0.001**
FEV1%predicted	-0.353	**< 0.001**	-0.136	0.536	-0.263	**0.009**
IC	-0.174	0.057	0.089	0.688	-0.267	**0.008**
%Dlco/VA	-0.165	0.071	0.202	0.356	-0.154	0.133
Chest HRCT						
LAA% for the upper lung field	0.046	0.617	-0.085	0.700	-0.075	0.465
Echocardiography						
LVDd	0.066	0.48	0.431	**0.040**	0.041	0.697
EF	0.194	0.036	0.593	**0.003**	0.145	0.164
E/A	-0.390	**< 0.001**	-0.657	**< 0.001**	-0.240	**0.021**
DT	0.299	**0.001**	0.488	**0.018**	0.246	**0.018**
E/E'	0.146	0.12	0.396	0.061	0.145	0.168
RVSP	0.202	**0.032**	0.274	0.229	0.169	0.108
CO	0.217	**0.019**	0.303	0.160	0.193	0.064
Six-minute walking test						
Walking distance	-0.444	**< 0.001**	-0.693	**< 0.001**	-0.393	**< 0.001**
Borg scale	0.348	**< 0.001**	0.231	0.289	0.324	**0.001**
Initiate SpO2	-0.054	0.56	0.006	0.979	0.014	0.894
Minimal SpO2	-0.168	0.067	-0.087	0.695	-0.104	0.312
Initiate PR	0.046	0.616	0.402	0.057	-0.059	0.566
Maximal PR	-0.157	0.086	-0.329	0.125	-0.103	0.314
Blood test						
hs-CRP	0.212	**0.002**	0.176	0.423	0.233	**0.021**
Gal-3	0.177	0.053	-0.032	0.887	0.163	0.111
NT-proBNP	0.437	**< 0.001**	0.206	0.346	0.454	**< 0.001**
SP-D	-0.011	0.908	-0.121	0.583	0.005	0.959
IL-6	0.490	**< 0.001**	0.594	**0.003**	0.453	**< 0.001**
CC16	0.120	0.190	0.051	0.819	0.182	0.074
sRAGE	-0.064	0.485	-0.332	0.122	0.047	0.650

Boldface indicates a *P* value with statistical significance. FVC; forced vital capacity, FEV1%; forced expiratory volume in 1 second, IC; inspiratory capacity, %DLco/VA; percent diffusing capacity of the lung for carbon monoxide/alveolar volume, HRCT; high-resolution computer tomography, LAA; percentage of low attenuation area, LVDd; left ventricular end-diastolic dimension, EF; ejection fraction, E/A; early diastolic filling velocity/atrial filling velocity ratio, DT; deceleration time, E/E'; early diastolic filling velocity/early diastolic mitral annular velocity, RVSP; right ventricular systolic pressure, CO; cardiac output, SpO2; oxygen saturation, PR; pulse rate, hs-CRP; high-sensitivity C-reactive protein, hs-TnT; high-sensitivity cardiac troponin T, NT-proBNP; N-terminal pro-brain natriuretic peptide, SP-D; surfactant protein D, IL-6; interleukin 6, CC16; club cell protein 16, sRAGE; soluble receptor for advanced glycation end products

patients, suggesting its utility in assessing exercise capacity. However, our study did not confirm Gal-3 as a predictive biomarker for cardiovascular comorbidities or further deterioration in COPD patients. Sundqvist et al. also found [24] that no significant correlation between systemic Gal-3 levels and COPD exacerbations, consistent with our findings. Although we did not observe significant elevations in Gal-3 levels among COPD patients with cardiovascular comorbidities, the correlation between Gal-3 and exercise-induced heart rate changes in our study aligns with previous research. Studies suggest that Gal-3 may play a role in autonomic regulation and myocardial stress during physical activity, indicating its potential importance in assessing cardiopulmonary function. For example, a previous study demonstrated [25] that elevated Gal-3 levels were associated with altered autonomic function and exercise capacity in heart failure patients, which may have parallels in COPD populations. Understanding this relationship could help identify COPD patients at greater risk for cardiovascular events during physical exertion, emphasizing the clinical relevance of monitoring Gal-3 levels.

Despite the findings that hs-cTnT may be a more sensitive biomarker for detecting cardiopulmonary changes, Gal-3 remains valuable for its role in myocardial fibrosis and inflammation. Our results support hs-TnT's potential as a more reliable indicator of cardiovascular disease in COPD patients compared to Gal-3. This biomarker

demonstrated significant correlations with multiple cardiopulmonary parameters, including FEV1%, walking distance, and markers of inflammation, highlighting its importance in clinical settings. In clinical settings, Gal-3 can aid in identifying patients at risk for developing cardiovascular comorbidities and provide insights into the extent of myocardial remodelling and fibrosis. Monitoring Gal-3 levels could potentially guide therapeutic interventions aimed at reducing inflammation and fibrosis, ultimately improving patient outcomes. Gal-3, monitored alongside hs-cTnT and NT-proBNP, could enhance cardiovascular risk assessment in COPD patients. Elevated Gal-3 levels may signal myocardial stress or fibrosis, complementing the sensitivity of hs-cTnT and NT-proBNP in detecting cardiac strain. This combined approach could support early detection and intervention, potentially improving outcomes. Its use alongside other biomarkers like hs-cTnT and NT-proBNP can provide a comprehensive evaluation of cardiovascular risk in COPD patients.

This study had several limitations. It was a single-centre study with a limited number of pre-COPD patients. Additionally, the absence of a healthy control group restricted our ability to directly compare biomarker levels between healthy individuals, cardiovascular disease patients, and COPD patients. Furthermore, there was a gender imbalance between the pre-COPD and COPD groups, which may impact the generalizability of the findings. Future longitudinal studies should incorporate healthy control data to provide a more comprehensive understanding the potential of Gal-3 as a biomarker. Increasing the sample size and including multiple centres in future studies could help validate our results. Moreover, the lack of a longitudinal follow-up limits our ability to evaluate the predictive value of Gal-3 over time and across different stages of COPD. Future studies should adopt a longitudinal approach to better understand the role of Gal-3, particularly in the progression from pre-COPD to COPD.

Conclusions

In conclusion, our study found that Gal-3 levels were related to NT-proBNP levels and heart rate response during exercise in both pre-COPD and stable COPD patients. However, we did not find sufficient evidence to support Gal-3 as a predictive biomarker for cardiovascular comorbidities or further deterioration in COPD patients, given the cross-sectional nature of our study. In contrast, hs-TnT levels showed stronger correlations with multiple cardiopulmonary function parameters, including age, FEV1%, E/A ratio, 6MWT distance, DT, RVSP, and hs-CRP, suggesting it's greater sensitivity as a biomarker for assessing cardiac function and predicting cardiovascular comorbidity in COPD populations. These results emphasize the need for larger cohort studies to validate the utility of hs-TnT as a more valuable biomarker in COPD management compared to Gal-3.

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Author contributions
KH conceptualized the study, designed the methodology, and conducted the primary analysis. TM and KM contributed to the data collection and assisted in the analysis and interpretation of the data. KM and KK provided critical revisions and intellectual content to the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All methods in this study were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice. This prospective study was approved by the ethics committee of Nippon Medical School (approval number: 28 – 16), and all patients provided written informed consent before enrolment.

Consent to publish
Not applicable.

Competing interests
The authors declare no competing interests.

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