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# ABSTRACT

## RHYTHM AND CONDUCTION DISORDERS IN PATIENTS WITH COVID-19

**ABSTRACT of a dissertation submitted for the award of the educational and scientific degree "Doctor" (PhD)**

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The dissertation was developed at the Department of Cardiology, Pulmonology and Endocrinology, Faculty of Medicine, Medical University – Pleven.

The study included 219 consecutive patients: 136 with a documented history of COVID-19 during the preceding six months and 83 control patients without such a history.

The abstract presents the aim, objectives, methodology, principal results, discussion, conclusions and scientific contributions of the dissertation.

The public defense of the dissertation will take place on September 29, 2026, at 14:00 in the Ambroise Paré Hall.

The dissertation materials are available for review at the Library of the Medical University – Pleven.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AH | arterial hypertension |
| PE | pulmonary embolism |
| DVT | deep vein thrombosis |
| RV | right ventricle |
| ECG | electrocardiogram |
| Echo | echocardiography |
| DM | diabetes mellitus |
| IHD | ischaemic heart disease |
| CK | creatine phosphokinase |
| CAD | coronary artery disease |
| CMP | cardiomyopathy |
| LV | left ventricle |
| LA | left atrium |
| MI | myocardial infarction |

| | |
|---|---|
| ACS | acute coronary syndrome |
| AF | atrial fibrillation |
| Permanent AF | permanent atrial fibrillation |
| AFL | atrial flutter |
| RAAS | renin–angiotensin–aldosterone system |
| RF | risk factor |
| HF | heart failure |
| CVD | cardiovascular diseases |
| EF | ejection fraction |
| Simpson-derived EF | ejection fraction calculated by the Simpson method |
| CKD | chronic kidney disease |
| COPD | chronic obstructive pulmonary disease |
| HVD | hypertensive vascular disease |

| | |
|---|---|
| ACE2 | angiotensin-converting enzyme 2 |
| AHA | American Heart Association |
| ARDS | acute respiratory distress syndrome |
| BMI | body mass index |
| CCL19 | C-C motif chemokine ligand 19 |
| CK | creatine kinase |
| CK-MB | creatine kinase MB fraction |
| CMR | cardiac magnetic resonance |
| COVID-19 | coronavirus disease 2019 |
| CRP | C-reactive protein |
| ECV | extracellular volume |
| EHRA | European Heart Rhythm Association |
| EMB | endomyocardial biopsy |
| ESC | European Society of Cardiology |
| GLS | global longitudinal strain |
| 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 |
| hs-cTn | high-sensitivity cardiac troponin |
| ICU | intensive care unit |
| IFN-γ | interferon gamma |
| IL | interleukin |
| LAVI | left atrial volume index |
| LGE | late gadolinium enhancement |
| LVEF | left ventricular ejection fraction |
| LVEDV | left ventricular end-diastolic volume |
| LVESV | left ventricular end-systolic volume |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| PCR | polymerase chain reaction |
| POTS | postural orthostatic tachycardia syndrome |
| ROC | receiver operating characteristic |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SPSS | Statistical Package for the Social Sciences |
| TAPSE | tricuspid annular plane systolic excursion |
| TNF-α | tumor necrosis factor alpha |

# I. INTRODUCTION

The COVID-19 pandemic and its cardiovascular consequences

At the end of 2019, the world faced a novel infectious disease caused by a new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which rapidly evolved into a global pandemic. The disease, known as coronavirus disease 2019 (COVID-19), was initially described as an acute respiratory syndrome; however, accumulating clinical and experimental evidence demonstrated that the infection is multisystemic and may affect numerous organs and systems, including the cardiovascular system (1,2).

SARS-CoV-2 belongs to the Coronaviridae family and is the seventh coronavirus known to infect humans. This family includes several viral strains, some causing severe disease and others producing milder upper respiratory tract infections. The former group includes SARS-CoV-1, the causative agent of severe acute respiratory syndrome in 2002–2003, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, whereas HKU1, NL63, OC43 and 229E generally cause milder respiratory infections (3). The term “coronavirus” derives from the characteristic morphology of viral particles, whose surface spike glycoproteins form a crown-like structure (4).

Although COVID-19 was initially regarded primarily as a respiratory infection, it gradually became evident that the disease has a substantial impact on the cardiovascular system. SARS-CoV-2 infection may cause a broad spectrum of cardiac complications, including myocardial injury, myocarditis, heart failure, thromboembolic complications, and rhythm and conduction disorders (5,6). The mechanisms of cardiac involvement are multifactorial and include direct viral invasion of cardiomyocytes, a systemic inflammatory response, endothelial dysfunction, and microcirculatory abnormalities (7).

Severe forms of COVID-19 are associated with substantial physiological stress on the myocardium. This stress results from a combination of pathological factors, including hypoxia, systemic inflammation, haemodynamic disturbances, and increased myocardial metabolic demand. In addition, activation of the sympathetic nervous system increases endogenous catecholamine levels, potentially causing adrenergic excess and contributing to electrophysiological changes in the myocardium (8). These processes may disrupt normal cardiac electrical activity and create a substrate for the development of different forms of cardiac arrhythmia (9).

Several clinical studies have shown that patients with pre-existing cardiovascular disease have a substantially higher risk of an adverse course of COVID-19. The most common comorbidities include arterial hypertension, coronary artery disease, diabetes mellitus, and chronic heart failure (10). In these patients, infection may cause decompensation of existing cardiac disease and the development of new cardiovascular complications.
In addition to acute cardiac manifestations, increasing attention has been directed towards the long-term cardiovascular consequences of COVID-19. Observations in patients who have recovered from the infection demonstrate persistent symptoms such as palpitations, tachycardia, reduced exercise capacity, and chest pain. Imaging studies, including cardiac magnetic resonance, frequently reveal myocardial oedema, inflammation, and interstitial fibrosis, which may create a structural substrate for rhythm and conduction disorders and chronic cardiac dysfunction (11).

These observations emphasise the importance of comprehensive investigation of cardiovascular complications in patients with COVID-19. Understanding the mechanisms of myocardial injury and arrhythmia development is essential for early diagnosis, appropriate clinical management, and optimisation of therapeutic strategies in these patients.

# II. AIM AND OBJECTIVES

## 1. Aim

The aim of the present dissertation was to analyse the association between previous SARS-CoV-2 infection and the development of cardiovascular complications, with emphasis on rhythm and conduction disorders, the biomarker profile of myocardial injury and haemodynamic load, and echocardiographic signs of structural and functional myocardial involvement. By comparing patients with a history of COVID-19 with a control group without such a history, the study sought to define a post-COVID cardiac phenotype characterised by a specific spectrum of arrhythmias, changes in ejection fraction, biochemical abnormalities, and evidence of remodelling.

## 2. Objectives

To achieve the stated aim, the following objectives were formulated:

1. To establish a cohort of patients with available clinical, laboratory and echocardiographic data enabling reliable comparative analysis between individuals with a history of COVID-19 confirmed by a positive PCR test and individuals without such a history.

2. To analyse the demographic characteristics of the study population, including age, sex, vaccination status, and major cardiovascular risk factors.

3. To assess the prevalence of comorbidities, including arterial hypertension, diabetes mellitus, renal dysfunction, obesity, family history, smoking, and alcohol use.

4. To describe the spectrum of rhythm and conduction disorders in the entire cohort and in subgroups by analysing the prevalence of paroxysmal, persistent and permanent atrial fibrillation, atrial flutter, premature ventricular complexes, ventricular tachycardia, sinus node dysfunction, and other arrhythmic phenotypes.

5. To investigate the association between a history of COVID-19 and the distribution of rhythm and conduction disorders.

6. To analyse the patients' laboratory profile by assessing lipid parameters, markers of myocardial injury, renal function, and electrolyte balance.

7. To investigate the values and distribution of troponin T, NT-proBNP, and Galectin-3 as biomarkers of acute or subacute myocardial injury, haemodynamic load, and inflammatory-fibrotic remodelling.

8. To compare echocardiographic parameters between the groups, with emphasis on left ventricular ejection fraction, left ventricular volumes, and parameters of diastolic function.

9. To assess correlations between biomarkers and echocardiographic parameters, and between biomarkers and renal function.

10. To identify independent predictors of reduced left ventricular systolic function and an adverse arrhythmic phenotype using multivariable statistical analysis.

11. To assess the discriminatory value of selected biomarkers for predicting an ejection fraction below 50% by ROC analysis.

12. To integrate clinical, electrocardiographic, laboratory and echocardiographic data into a unified analytical framework describing post-COVID cardiac involvement.

# III. MATERIALS AND METHODS

## 3.1 Study design

The present study was a retrospective, observational, comparative cohort study based on consecutively included patients with available demographic, clinical, laboratory and echocardiographic data. The analytical framework was aligned with the principal scientific hypothesis that previous SARS-CoV-2 infection is associated with changes in the spectrum of rhythm and conduction disorders, differences in biomarker profiles, and signs of structural and functional myocardial involvement.

The study was comparative and included two principal groups: a study group of patients with a documented history of COVID-19 and a positive PCR test within the preceding six months, and a control group without such a history. All analyses were performed using real-world data obtained from the available clinical records and working database.

## 3.2 Patient selection

A total of 219 consecutive patients who underwent cardiological assessment were included, provided that sufficient data were available for analysis of rhythm and conduction disorders, laboratory profile, and echocardiographic parameters. The patients were allocated to two groups according to COVID-19 history: 136 patients with evidence of previous COVID-19 infection during the preceding six months and 83 patients without evidence of such infection.

Patients were selected consecutively from the available database to minimise selection bias. Cohort formation followed a predefined logic requiring the simultaneous availability of demographic data, information on major comorbidities, laboratory parameters, and Simpson-derived ejection fraction. The number of valid observations differed for some variables and was accounted for in each individual analysis.

## 3.3 Inclusion criteria:

- available age and sex data;
- documented COVID-19 status: a history of infection during the preceding six months or absence of such a history;

- available laboratory parameters, including at least some of the following: LDL cholesterol, triglycerides, total cholesterol, troponin T, creatinine, urea, CK, CK-MB, potassium, sodium, NT-proBNP, and Galectin-3;
- available echocardiographic assessment with Simpson-derived ejection fraction;
- available information on a previous and/or current rhythm or conduction event.

3.4 Exclusion criteria

- insufficient clinical or laboratory data for inclusion in the planned between-group comparison;
- absence of echocardiographic assessment of ejection fraction;
- absence of data permitting classification according to COVID-19 history;
- duplicate records or records with internally inconsistent data precluding reliable interpretation.

3.5 Data sources and database processing

Data were extracted from the available clinical documentation and working database, which included demographic variables, COVID-19 status, vaccination status, comorbidities, laboratory parameters, echocardiographic indices, and descriptions of rhythm and conduction events.

Binary codes in the working database were interpreted according to the internal logic of the dataset. Predefined coding was used for variables such as vaccination status, family history, smoking, and alcohol use. For variables with missing values, such as obesity, analyses were performed using available cases, and missing values were not mechanically imputed.

3.6 Definitions of clinical and analytical variables

A history of COVID-19 was defined as documented SARS-CoV-2 infection during the preceding six months, as recorded in the clinical documentation and analytical database. The control group included patients without a documented history of COVID-19 during the same period.

For the purposes of multivariable analysis, an adverse arrhythmic phenotype was defined as permanent or persistent atrial fibrillation, atrial flutter, ventricular tachycardia, or sinus node

dysfunction. This composite endpoint was selected to combine clinically more severe rhythm and conduction disorders into a single binary variable.

Reduced left ventricular systolic function was defined as a left ventricular ejection fraction below 50%. For descriptive and stratified analyses, ejection fraction was additionally categorised into three groups: below 40%, 40–49%, and 50% or higher.

Renal function was assessed using serum creatinine and urea values and, in the extended Galectin-3 analysis, by eGFR category when available. Diabetes status was analysed in three categories: no diabetes, established diabetes, and newly diagnosed diabetes.

### 3.7 Medical history and clinical assessment

Available historical data on cardiovascular risk factors and comorbidities were analysed in all patients. These included age, sex, family history, smoking, alcohol use, diabetes mellitus, arterial hypertension/hypertensive vascular disease, obesity, and evidence of heart failure. These variables were used both for descriptive characterisation of the cohort and as potential confounders in the regression models.

### 3.8 Electrocardiography and arrhythmia assessment

The arrhythmia profile was extracted from the available clinical documentation and electronic database, in which the previous and/or current rhythm or conduction event had been described.

For analysis, the following principal arrhythmia categories were formed: paroxysmal/recurrent atrial fibrillation, permanent/persistent atrial fibrillation, atrial flutter, premature ventricular complexes, ventricular tachycardia, sinus node dysfunction, other arrhythmias, and unspecified previous events. When evidence of a previous rhythm or conduction episode was available, it was analysed separately as a binary or multicategorical variable.

Available electrocardiographic and Holter monitoring data were interpreted according to standard clinical criteria.

### 3.9 Echocardiographic examination

Echocardiographic assessment was a core component of the present study because it enabled objective evaluation of structural and functional myocardial involvement in patients

with and without a history of COVID-19. The analysis was based on standard transthoracic echocardiographic examinations documented in the available clinical database.

The principal echocardiographic parameter was left ventricular ejection fraction determined by the Simpson method. This parameter was used both as a continuous variable and as a categorical variable in three clinically meaningful ranges: LVEF <40%, LVEF 40–49%, and LVEF ≥50%. This permitted assessment of the overall distribution of systolic function and clinical stratification according to the severity of left ventricular dysfunction.

The analysis also included left ventricular end-diastolic and end-systolic volumes, which were used to evaluate remodelling. In the extended Galectin-3 analysis, parameters of diastolic function such as E/e′ and indices of left atrial volume were also interpreted because they reflect filling pressures, left atrial remodelling, and chronic haemodynamic load.

Echocardiographic data were used for several analytical purposes: between-group comparison of the COVID-19 and control groups; phenotyping according to arrhythmia type; correlation analysis with biomarkers; and as a component of the composite model of the cardiac remodelling phenotype. Echocardiography was therefore regarded not merely as a descriptive method but as a central instrument for pathophysiological interpretation.

### 3.10 Laboratory and biomarker parameters

Laboratory analysis included several principal groups of parameters: lipid profile, markers of myocardial injury, markers of haemodynamic load, indices of renal function, and electrolytes. LDL cholesterol, triglycerides, total cholesterol, troponin T, creatinine, urea, creatine kinase, CK-MB, potassium, and sodium were assessed. According to the available database, troponin T was analysed as a quantitative variable, whereas NT-proBNP was analysed as an ordinal categorical biomarker within predefined ranges.

Galectin-3 was included as a biomarker and analysed as a continuous variable. It was used for comparison between the COVID-19 and control groups, stratification by clinical modifiers, correlation analysis with NT-proBNP, troponin, echocardiographic parameters and renal function, and as an independent variable in a multivariable logistic model. Galectin-3 was therefore regarded as a marker of inflammatory-fibrotic remodelling rather than solely as a descriptive laboratory parameter.

NT-proBNP was interpreted as a biomarker of haemodynamic load. Because categorical values were available in the working table, it was analysed by within-group stratification

according to ejection fraction and was also incorporated into the extended Galectin-3 model. This enabled integration of NT-proBNP into the biomarker profile of post-COVID involvement.

### 3.11 Analytical endpoints

The principal analytical endpoints were not time-to-event outcomes but structural-functional and phenotypic characteristics. The first primary endpoint was reduced left ventricular systolic function, defined as LVEF <50%. The second was the presence of an adverse arrhythmic phenotype. The extended Galectin-3 analysis used a third endpoint: a cardiac remodelling phenotype defined by heart failure and/or a combination of reduced LVEF, dilated left ventricular volumes, and abnormal indices of diastolic dysfunction.

### 3.12 Statistical methods

Statistical processing was performed in several consecutive stages according to variable type, data distribution, and the analytical purpose of each model. Quantitative variables were presented as mean and standard deviation for approximately normal distributions and as median and interquartile range for asymmetric distributions. Categorical variables were described using absolute frequencies and relative percentages.

The distribution of continuous variables was assessed by examining distribution shape, and non-parametric approaches were used when marked asymmetry was present, because a substantial proportion of biomarkers and biochemical parameters showed right-skewed distributions. Between-group comparisons of two independent groups were performed mainly using the Mann–Whitney test. Comparisons of more than two independent groups, including arrhythmia phenotypes, were performed using the Kruskal–Wallis test.

Categorical variables were compared between the COVID-19 and control groups and between rhythm and conduction phenotype subgroups using the $\chi^2$ test. Fisher's exact test was applied where expected cell counts were small. These methods were used to assess distributions by sex, family history, diabetes mellitus, smoking, alcohol use, obesity, and NT-proBNP categories.

Correlation analysis was performed using Spearman's coefficient ($\rho$), because the principal biomarkers and some echocardiographic parameters were not normally distributed. This approach assessed associations between troponin T and ejection fraction, CK-MB and

troponin T, renal function and left ventricular systolic function, and Galectin-3 and NT-proBNP, troponin, left ventricular volumes, E/e′, LAVI, and eGFR.

Multivariable logistic regression was used to identify independent predictors. In the first model, the dependent variable was reduced left ventricular systolic function (LVEF <50%). Age, sex, history of COVID-19, diabetes mellitus, LDL, CK-MB, creatinine, and log-transformed troponin T were included. Results were reported as odds ratios (ORs) with 95% confidence intervals.

In the second logistic model, the dependent variable was the adverse arrhythmic phenotype. Independent variables included age, sex, COVID-19 status, diabetes, LDL, log-transformed troponin T, creatinine, and ejection fraction. Ejection fraction was modelled per 10-percentage-point increase to provide a clinically interpretable estimate of its effect on arrhythmic risk.

In the extended Galectin-3 module, a separate multivariable logistic model evaluated the independent predictive value of Galectin-3 for a cardiac remodelling phenotype. The model included Galectin-3, NT-proBNP, high-sensitivity troponin, eGFR, age, diabetes mellitus, obesity, and background heart failure. The purpose was to distinguish the independent contribution of Galectin-3 from the effects of renal function, age, metabolic risk, and haemodynamic load.

ROC analysis was performed to assess the discriminatory ability of selected biomarkers for reduced left ventricular systolic function. Areas under the ROC curve (AUCs) were calculated for troponin T, CK-MB, creatinine, and LDL, enabling comparative evaluation of their diagnostic information.

Statistical significance was accepted at $p < 0.05$. Analyses were performed using specialised statistical software. Results were presented by separating descriptive statistics from analyses of associations and independent predictors, allowing logical and transparent interpretation.

### 3.13 Ethical considerations and methodological limitations

The study was retrospective and based on previously available clinical data. Owing to this design, no intervention was made in the diagnostic or therapeutic process. The analysis was conducted for scientific purposes and complied with requirements for confidentiality and de-identification of patient data.

The principal methodological limitations arose from the retrospective design, the varying number of available observations for individual variables, and partial heterogeneity of the primary documentation. Nevertheless, the database structure permitted reliable comparative and correlation analyses and multivariable modelling, enabling valid conclusions regarding post-COVID cardiac involvement and its association with rhythm and conduction disorders.

# IV. RESULTS

The analysis included 219 consecutive patients with available demographic, clinical, laboratory and echocardiographic data. The final database contained information on a history of COVID-19 during the preceding six months, vaccination status, cardiometabolic comorbidities, lipid profile, markers of myocardial injury, renal function, electrolytes, Simpson-derived ejection fraction, and previous and/or current rhythm or conduction events.

Statistical approach. Absolute frequencies and percentages are presented for categorical variables. Continuous variables are presented as mean ± standard deviation and median with interquartile range. Comparisons between two independent groups were performed using the Mann–Whitney test, and comparisons among more than two groups using the Kruskal–Wallis test. Categorical variables were compared using the $\chi^2$ test. Correlations were assessed using Spearman's ρ. Logistic regression models were additionally constructed for predictors of LVEF <50% and an adverse arrhythmic phenotype. ROC analysis was used to evaluate the discriminatory value of selected biomarkers for reduced left ventricular systolic function.

## 4.1 Characteristics of the study population

The mean age of the entire cohort was 65.71 ± 14.22 years, with a median of 67 years [IQR 59–76]. There were 114 men (52.1%) and 105 women (47.9%). A history of COVID-19 during the preceding six months was present in 136 patients (62.1%), and documented vaccination in 19 (8.7%).

*Table 1. Principal demographic and COVID-19 characteristics of the cohort.*

| Parameter | n | % |
|---|---|---|
| History of COVID-19 | 136 | 136 (62.1%) |
| No history of COVID-19 | 83 | 83 (37.9%) |
| Men | 114 | 114 (52.1%) |
| Women | 105 | 105 (47.9%) |
| Vaccinated against COVID-19 | 19 | 19 (8.7%) |
| | | |

The COVID-19 group comprised 136 patients (62.1%), and the control group without COVID-19 comprised 83 patients (37.9%). Mean age was 64.75 ± 13.58 years in the COVID-19 group and 67.24 ± 15.16 years in the control group. The age difference did not reach statistical significance ($p = 0.071$).

*Table 2. Demographic characteristics according to COVID-19 history.*

| Group | n | Women | Men | Age, mean ± SD | Median [IQR] |
|---|---|---|---|---|---|
| History of COVID-19 | 136 | 60 (44.1%) | 76 (55.9%) | 64.75 ± 13.58 | 65.00 [58.25-74.75] |
| No history of COVID-19 | 83 | 45 (54.2%) | 38 (45.8%) | 67.24 ± 15.16 | 71.00 [59.50-81.00] |
| Total | 219 | 105 (47.9%) | 114 (52.1%) | 65.71 ± 14.22 | 67.00 [59.00-76.00] |

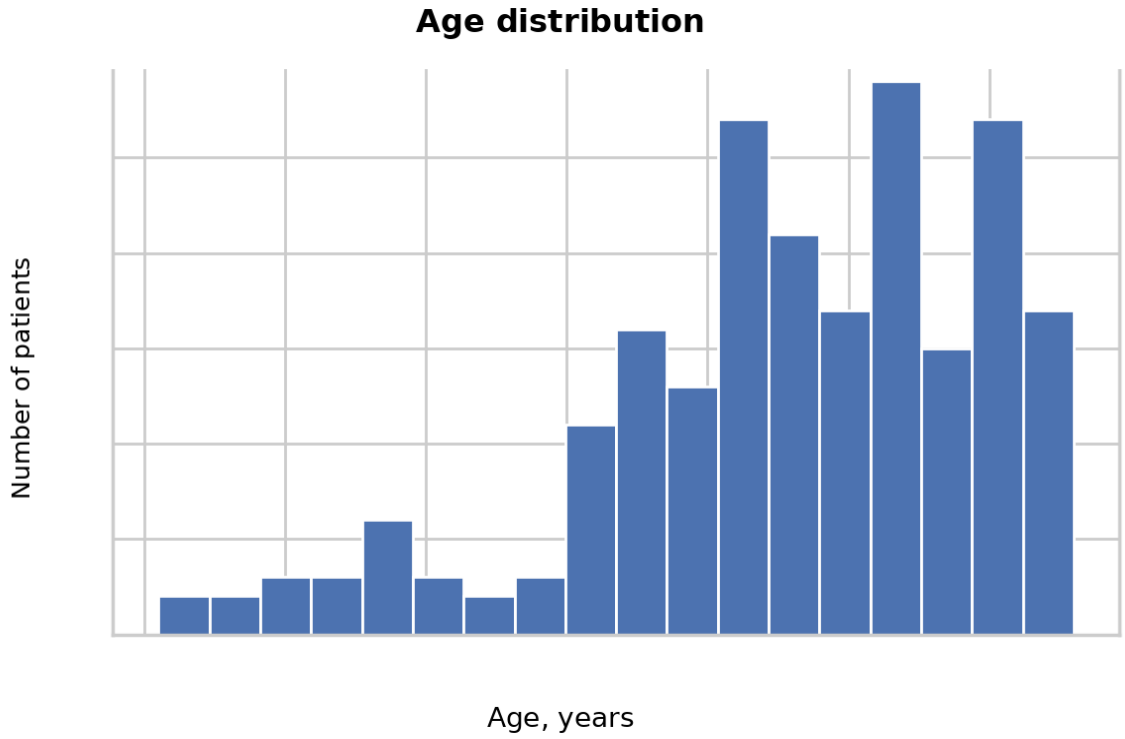


*Figure 1. Age distribution of the study population.*

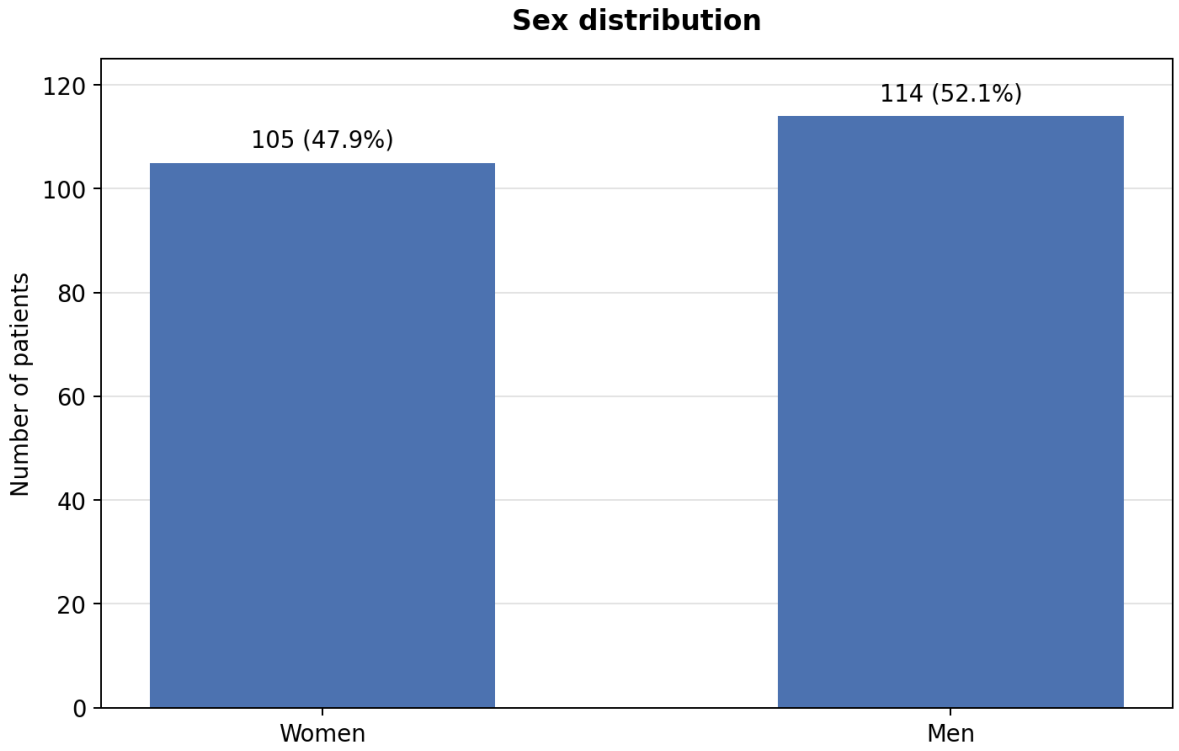


*Figure 2. Sex distribution.*

*Table 3. Age characteristics according to COVID-19 history; p for age = 0.071.*

| Group | n | Age, mean ± SD | Median [IQR] |
|---|---|---|---|
| History of COVID-19 | 136 | 64.75 ± 13.58 | 65.00 [58.25–74.75] |
| No history of COVID-19 | 83 | 67.24 ± 15.16 | 71.00 [59.50–81.00] |
| Total | 219 | 65.71 ± 14.22 | 67.00 [59.00–76.00] |

4.2 COVID-19 characteristics

Comparison of patients with and without a history of COVID-19 revealed no statistically significant difference in age (p = 0.071) or sex distribution ($\chi^2$ p = 0.190). There was only a trend towards younger age in the COVID-19 group (median 65 versus 71 years). Vaccination was documented relatively infrequently and showed no significant association with COVID-19 group allocation (p = 0.181).

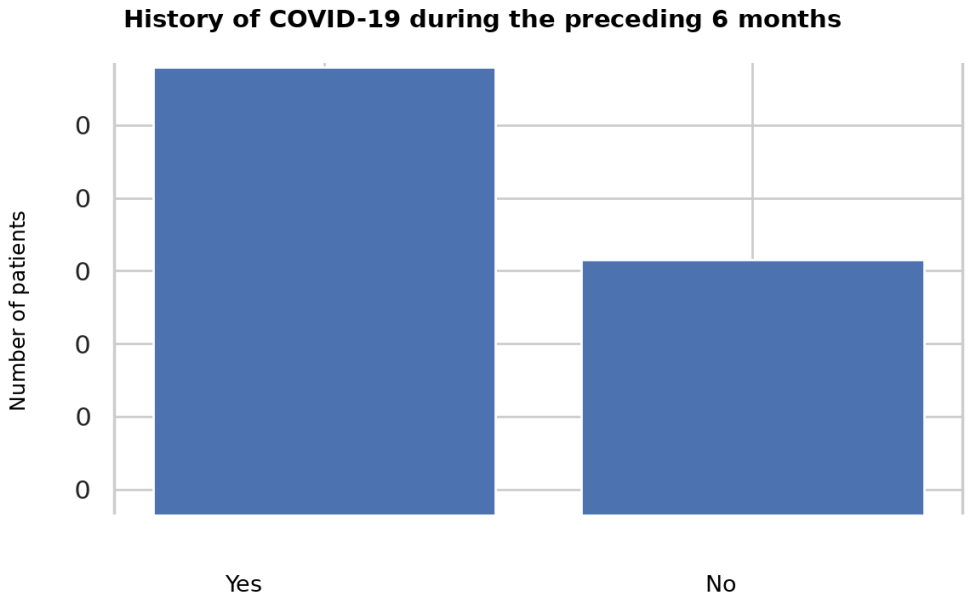


*Figure 3. Distribution of the cohort according to history of COVID-19.*

4.3 Comorbidities and risk factors

The most common comorbidity was grade III hypertensive vascular disease, present in 148 patients (67.6% of the entire cohort). Diabetes mellitus or newly diagnosed diabetes was present in 67 patients (30.6%), active smoking in 87 (39.7%), and a history of alcohol use in 20 (9.1%). Obesity was explicitly recorded in only six patients, whereas information was missing in 103 cases.

*Table 4. Risk factors and comorbidities according to history of COVID-19.*

| Parameter | Category | COVID | No COVID-19 | Total | p |
|---|---|---|---|---|---|
| Sex | Female | 60 (44.1%) | 45 (54.2%) | 105 (47.9%) | 0.190 |
| Sex | Male | 76 (55.9%) | 38 (45.8%) | 114 (52.1%) | |
| Family history | Yes | 14 (10.3%) | 8 (9.6%) | 22 (10.0%) | 1.000 |
| Family history | No | 122 (89.7%) | 75 (90.4%) | 197 (90.0%) | |
| Diabetes mellitus | Yes | 34 (25.0%) | 27 (32.5%) | 61 (27.9%) | 0.133 |
| Diabetes mellitus | No | 100 (73.5%) | 52 (62.7%) | 152 (69.4%) | |

| | | | | | |
|---|---|---|---|---|---|
| Diabetes mellitus | Newly diagnosed | 2 (1.5%) | 4 (4.8%) | 6 (2.7%) | |
| HVD | Grade I | 8 (5.9%) | 4 (4.8%) | 12 (5.5%) | 0.752 |
| HVD | Grade II | 28 (20.6%) | 13 (15.7%) | 41 (18.7%) | |
| HVD | Grade III | 92 (67.6%) | 56 (67.5%) | 148 (67.6%) | |
| Smoking | Yes | 57 (41.9%) | 30 (36.1%) | 87 (39.7%) | 0.482 |
| Smoking | No | 79 (58.1%) | 53 (63.9%) | 132 (60.3%) | |
| Alcohol use | Yes | 13 (9.6%) | 7 (8.4%) | 20 (9.1%) | 0.969 |
| Alcohol use | No | 123 (90.4%) | 76 (91.6%) | 199 (90.9%) | |
| Obesity | Yes | 6 (4.4%) | 0 (0.0%) | 6 (2.7%) | |
| Obesity | No | 64 (47.1%) | 46 (55.4%) | 110 (50.2%) | |
| | | | | | |

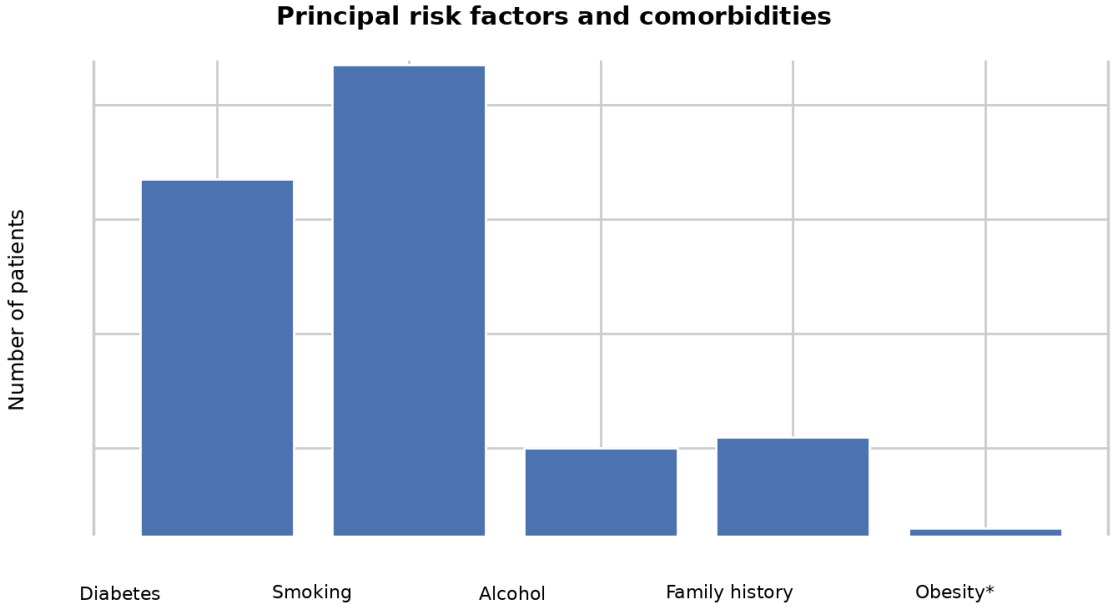


*Figure 4. Principal risk factors and comorbidities in the entire cohort.*

4.4 Spectrum of rhythm and conduction disorders

The current arrhythmic phenotype was extracted from the free-text field following the key phrase "currently – …". The most frequent phenotype was paroxysmal/recurrent atrial fibrillation in 106 patients (48.4%), followed by permanent/persistent atrial fibrillation in 43

(19.6%), premature ventricular complexes in 20 (9.1%), and atrial flutter in 16 (7.3%). A previous rhythm or conduction event was documented in 71 patients (32.4%).

*Table 5. Distribution of the current arrhythmic phenotype.*

| Current arrhythmic phenotype | n | % |
|---|---|---|
| Paroxysmal/recurrent AF | 106 | 48.4% |
| Permanent/persistent AF | 43 | 19.6% |
| Premature ventricular complexes | 20 | 9.1% |
| Atrial flutter | 16 | 7.3% |
| Sinus node dysfunction | 11 | 5.0% |
| Unspecified previous event | 8 | 3.7% |
| Ventricular tachycardia | 7 | 3.2% |
| Other/non-arrhythmic | 6 | 2.7% |
| Other arrhythmias | 2 | 0.9% |

*Table 6. Previous rhythm or conduction event.*

| Previous rhythm or conduction event | n | % |
|---|---|---|
| No | 134 | 61.2% |
| Yes | 71 | 32.4% |
| Other | 10 | 4.6% |
| No data | 4 | 1.8% |

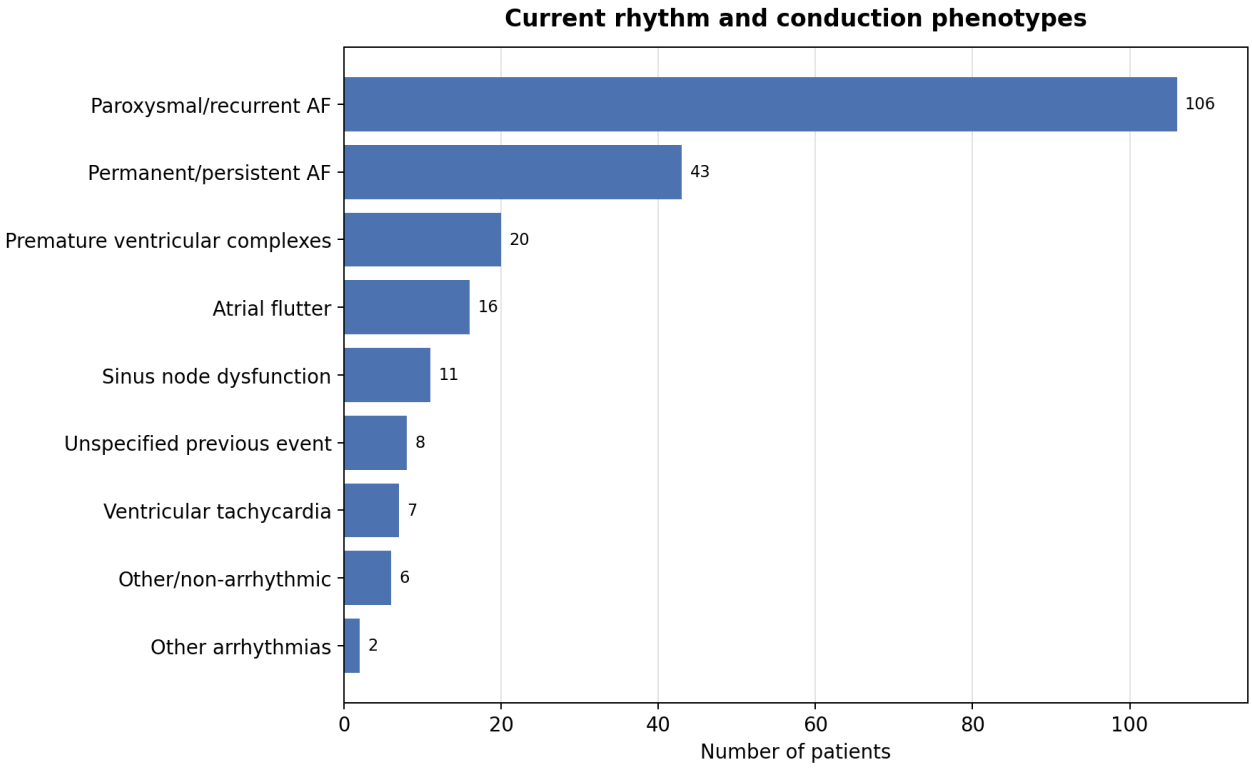


*Figure 5. Detailed distribution of the arrhythmic phenotype.*

4.5 Laboratory and echocardiographic profile

In the entire cohort, the median troponin T concentration was 0.01 ng/mL [0.01–0.03], median CK-MB was 18.68 U/L [14.30–25.00], median creatinine was 84 µmol/L [72–105], and median Simpson-derived ejection fraction was 0.56 [0.52–0.60]. Potassium and sodium values were extracted from a combined free-text column and enabled additional electrolyte profiling.

*Table 7. Overall descriptive statistics for continuous variables.*

| Parameter | n | Mean ± SD | Median [IQR] | Min–max |
|---|---|---|---|---|
| Age, years | 217 | 65.71 ± 14.22 | 67.00 [59.00–76.00] | 21.00–86.00 |
| LDL | 206 | 3.01 ± 1.16 | 2.92 [2.21–3.75] | 0.53–6.75 |
| TG | 201 | 1.75 ± 1.56 | 1.35 [0.98–1.84] | 0.35–13.25 |
| Total cholesterol | 203 | 5.02 ± 1.40 | 4.93 [4.06–5.78] | 1.89–9.61 |
| Troponin T /0.012/ | 205 | 0.04 ± 0.15 | 0.01 [0.01–0.03] | 0.00–1.50 |
| Creatinine | 217 | 98.55 ± 79.16 | 84.00 [72.00–105.00] | 47.00–850.00 |
| Urea | 203 | 7.68 ± 5.22 | 6.50 [5.00–8.80] | 2.50–61.00 |
| CK | 214 | 138.38 ± 122.51 | 113.00 [74.00–170.00] | 1.25–1280.00 |

| | | | | |
|---|---|---|---|---|
| CK-MB | 209 | 20.63 ± 9.40 | 18.68 [14.30–25.00] | 8.20–74.00 |
| K | 217 | 4.34 ± 0.52 | 4.30 [4.00–4.60] | 3.32–6.50 |
| Na | 217 | 141.09 ± 4.47 | 142.00 [139.00–144.00] | 115.00–149.00 |
| Simpson-derived EF | 217 | 55% ± 0.08 | 56% [52–60] | 26%–71% |

Comparison according to COVID-19 history demonstrated statistically significant differences in LDL (p = 0.042), triglycerides (p = 0.012), total cholesterol (p = 0.022), and CK-MB (p = 0.024). The lipid profile was less favourable in the COVID-19 group, whereas median CK-MB was lower than in the group without a history of COVID-19 (17.20 versus 20.00 U/L). Troponin T and Simpson-derived LVEF did not differ significantly.

*Table 8. Laboratory and echocardiographic parameters according to history of COVID-19.*

| Parameter | COVID-19 mean ± SD | COVID-19 median [IQR] | No COVID-19 mean ± SD | No COVID-19 median [IQR] | p |
|---|---|---|---|---|---|
| LDL | 3.12 ± 1.21 | 3.16 [2.27–3.84] | 2.82 ± 1.06 | 2.59 [2.09–3.49] | 0.042 |
| TG | 1.89 ± 1.77 | 1.51 [1.03–1.84] | 1.51 ± 1.08 | 1.12 [0.92–1.82] | 0.012 |
| Total cholesterol | 5.19 ± 1.42 | 5.21 [4.31–5.81] | 4.74 ± 1.31 | 4.60 [3.82–5.78] | 0.022 |
| Troponin T /0.012/ | 0.04 ± 0.19 | 0.01 [0.01–0.03] | 0.03 ± 0.06 | 0.02 [0.01–0.04] | 0.635 |
| Creatinine | 104.98 ± 97.69 | 87.00 [73.03–102.50] | 88.17 ± 29.17 | 81.00 [66.00–110.00] | 0.068 |
| Urea | 7.41 ± 3.73 | 6.50 [5.00–8.07] | 8.13 ± 7.08 | 6.50 [5.10–10.00] | 0.745 |
| CK | 143.96 ± 133.94 | 117.00 [83.75–179.25] | 129.39 ± 101.59 | 111.00 [68.00–144.00] | 0.245 |
| CK-MB | 19.82 ± 9.82 | 17.20 [14.20–22.23] | 21.89 ± 8.61 | 20.00 [14.30–27.10] | 0.024 |
| K | 4.33 ± 0.45 | 4.25 [4.10–4.59] | 4.37 ± 0.63 | 4.30 [3.80–4.70] | 0.933 |
| Na | 140.83 ± 5.03 | 142.00 [139.00–144.00] | 141.51 ± 3.37 | 141.00 [139.00–144.00] | 0.753 |
| Simpson-derived EF | 55% ± 0.08 | 56% [52–61] | 54% ± 0.09 | 56% [0.52–0.60] | 0.629 |

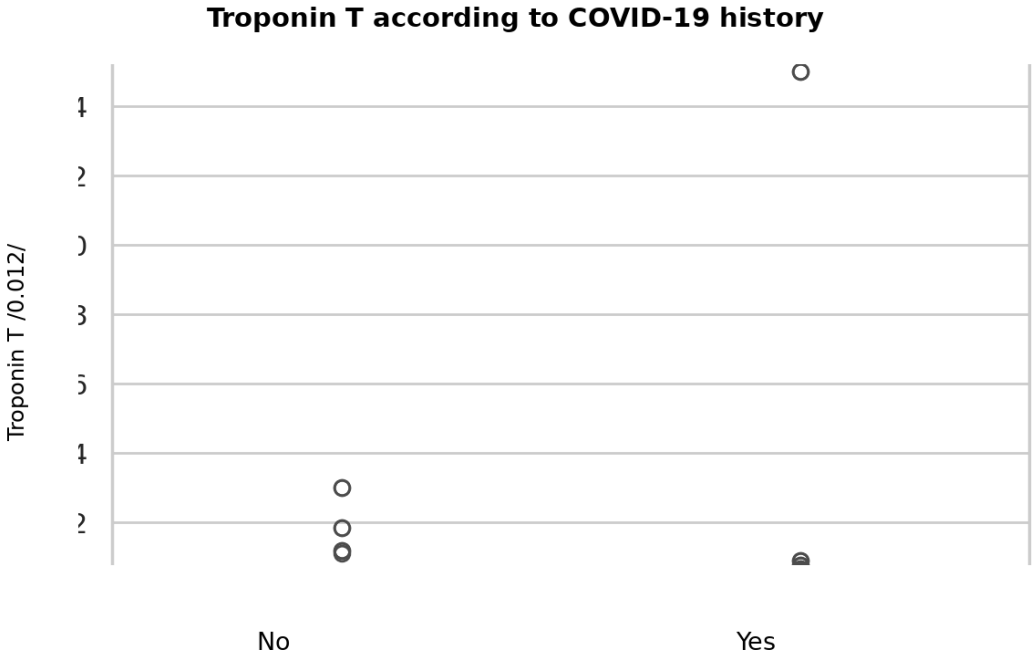


*Figure 6. Troponin T according to history of COVID-19.*

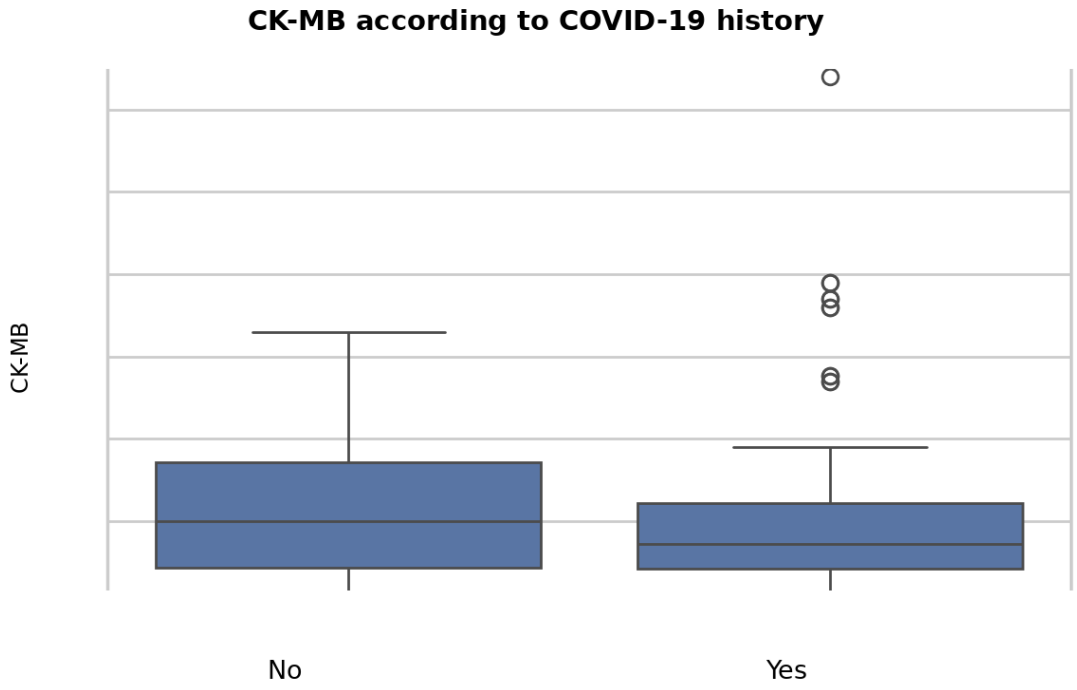


*Figure 7. CK-MB according to history of COVID-19.*

### 4.6 Parameters according to arrhythmia type

For more detailed phenotypic analysis, the five most frequent arrhythmia groups were examined: paroxysmal/recurrent atrial fibrillation, permanent/persistent atrial fibrillation, atrial flutter, premature ventricular complexes, and sinus node dysfunction. Highly significant differences were observed among these groups for age ($p < 0.001$), troponin T ($p < 0.001$), creatinine ($p = 0.007$), urea ($p < 0.001$), triglycerides ($p = 0.036$), and Simpson-derived LVEF ($p < 0.001$). Permanent/persistent atrial fibrillation was characterised by the highest mean age and lowest mean LVEF, whereas sinus node dysfunction occurred in a younger population with relatively preserved left ventricular function.

*Table 9. Continuous variables according to the principal arrhythmic phenotypes.*

| Parameter | Paroxysmal/recurrent AF | Permanent/persistent AF | Atrial flutter | Premature ventricular complexes | Sinus node dysfunction | p |
|---|---|---|---|---|---|---|
| Age, years | 65.42 ± 12.25 | 75.95 ± 8.02 | 66.38 ± 7.78 | 61.05 ± 14.52 | 49.45 ± 20.66 | <0.001 |
| TG | 1.58 ± 0.88 | 1.51 ± 1.02 | 2.25 ± 1.61 | 1.84 ± 1.39 | 1.09 ± 0.55 | 0.036 |
| Troponin T /0.012/ | 0.05 ± 0.21 | 0.03 ± 0.02 | 0.03 ± 0.03 | 0.04 ± 0.09 | 0.02 ± 0.02 | <0.001 |
| Creatinine | 87.78 ± 32.56 | 99.47 ± 27.90 | 101.75 ± 29.11 | 86.50 ± 15.49 | 73.91 ± 19.20 | 0.007 |
| Urea | 7.11 ± 5.90 | 9.04 ± 3.71 | 7.42 ± 2.51 | 6.57 ± 1.47 | 5.52 ± 2.27 | <0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Simpson-derived EF | 56% ± 0.07 | 50% ± 0.08 | 50% ± 0.07 | 57% ± 0.09 | 60% ± 0.07 | <0.001 |

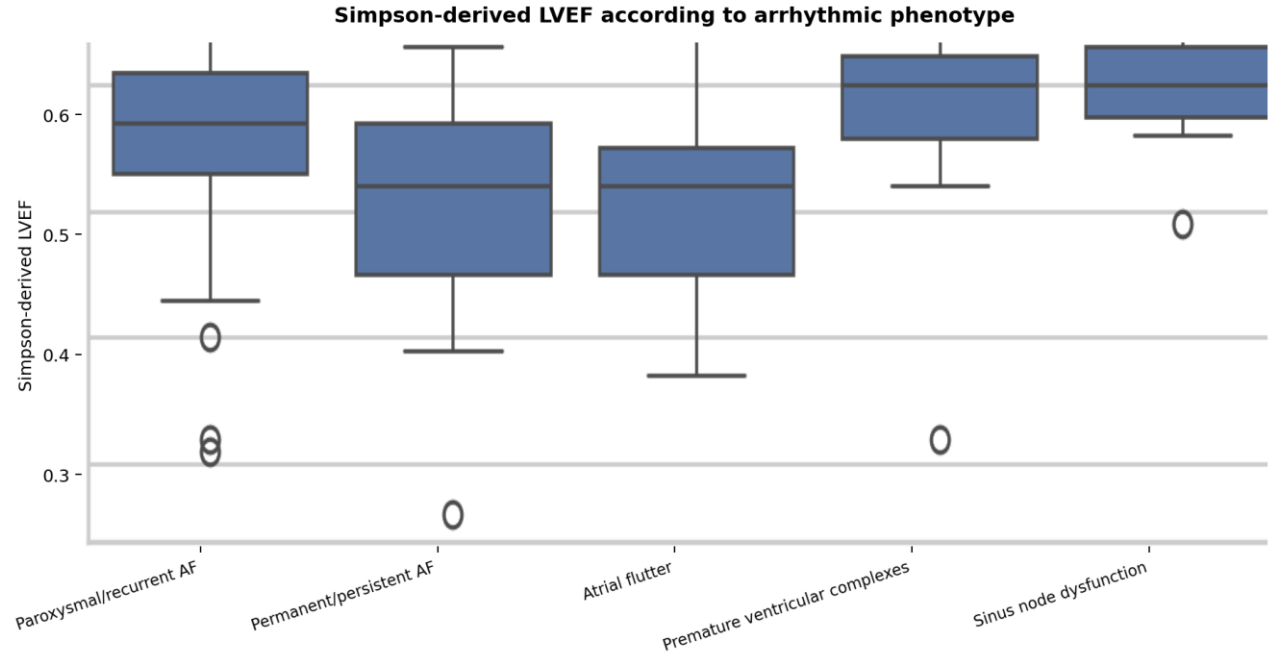


*Figure 8. Simpson-derived LVEF according to arrhythmic phenotype. (0.3 = 30%, 0.4 = 40%, 0.5 = 50%, 0.6 = 60%, 0.7 = 70%).*

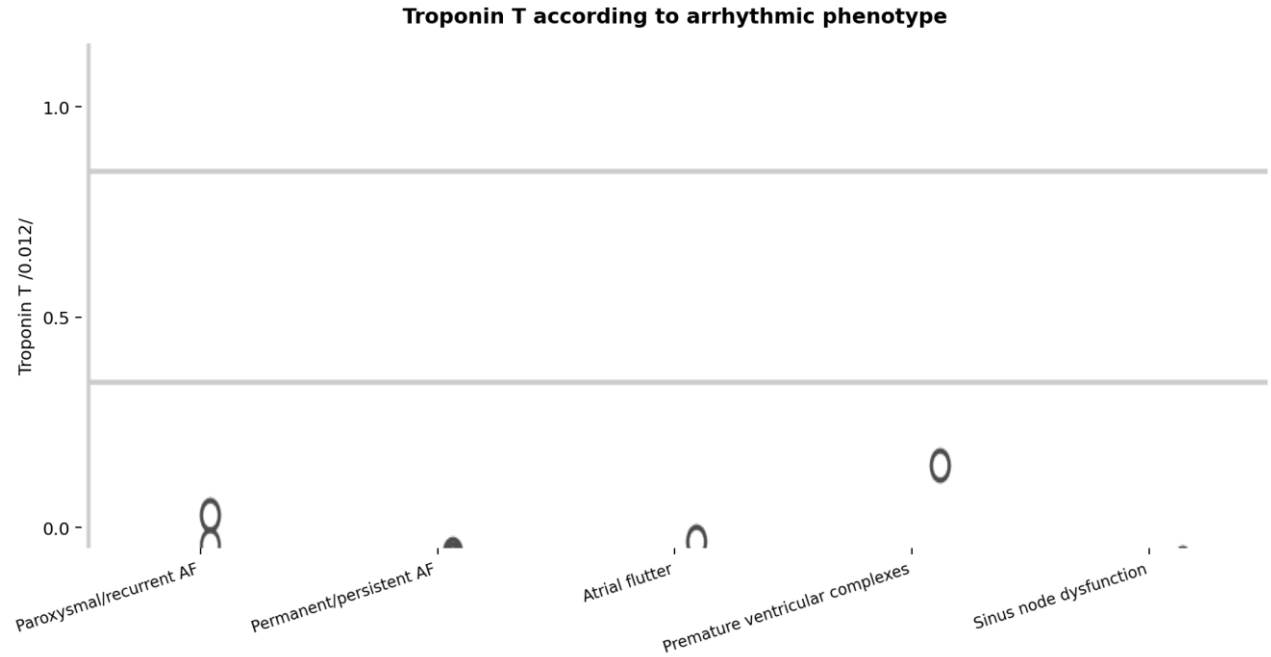


*Figure 9. Troponin T according to arrhythmic phenotype.*

4.7 Correlation analysis

Correlation analysis demonstrated a statistically significant inverse association between troponin T and Simpson-derived ejection fraction, as well as weaker but consistent negative associations between indices of renal dysfunction and left ventricular systolic function.

*Table 10. Spearman correlations between biomarkers, renal function, and Simpson-derived LVEF.*

| Variable 1 | Variable 2 | n | Spearman ρ | p |
|---|---|---|---|---|
| Troponin T /0.012/ | Simpson-derived EF | 205 | -0.270 | <0.001 |
| CK-MB | Troponin T /0.012/ | 205 | 0.162 | 0.020 |
| Creatinine | Simpson-derived EF | 217 | -0.141 | 0.038 |
| LDL | Simpson-derived EF | 204 | 0.234 | <0.001 |
| Urea | Simpson-derived EF | 203 | -0.218 | 0.002 |
| CK-MB | Simpson-derived EF | 209 | -0.073 | 0.290 |

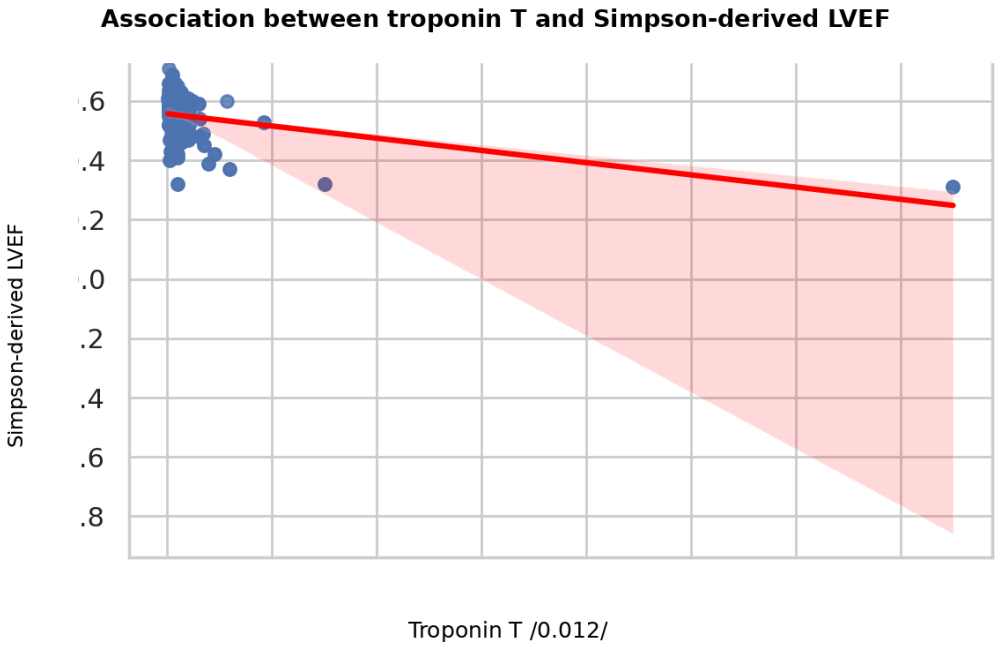


*Figure 10. Association between troponin T and Simpson-derived LVEF.*

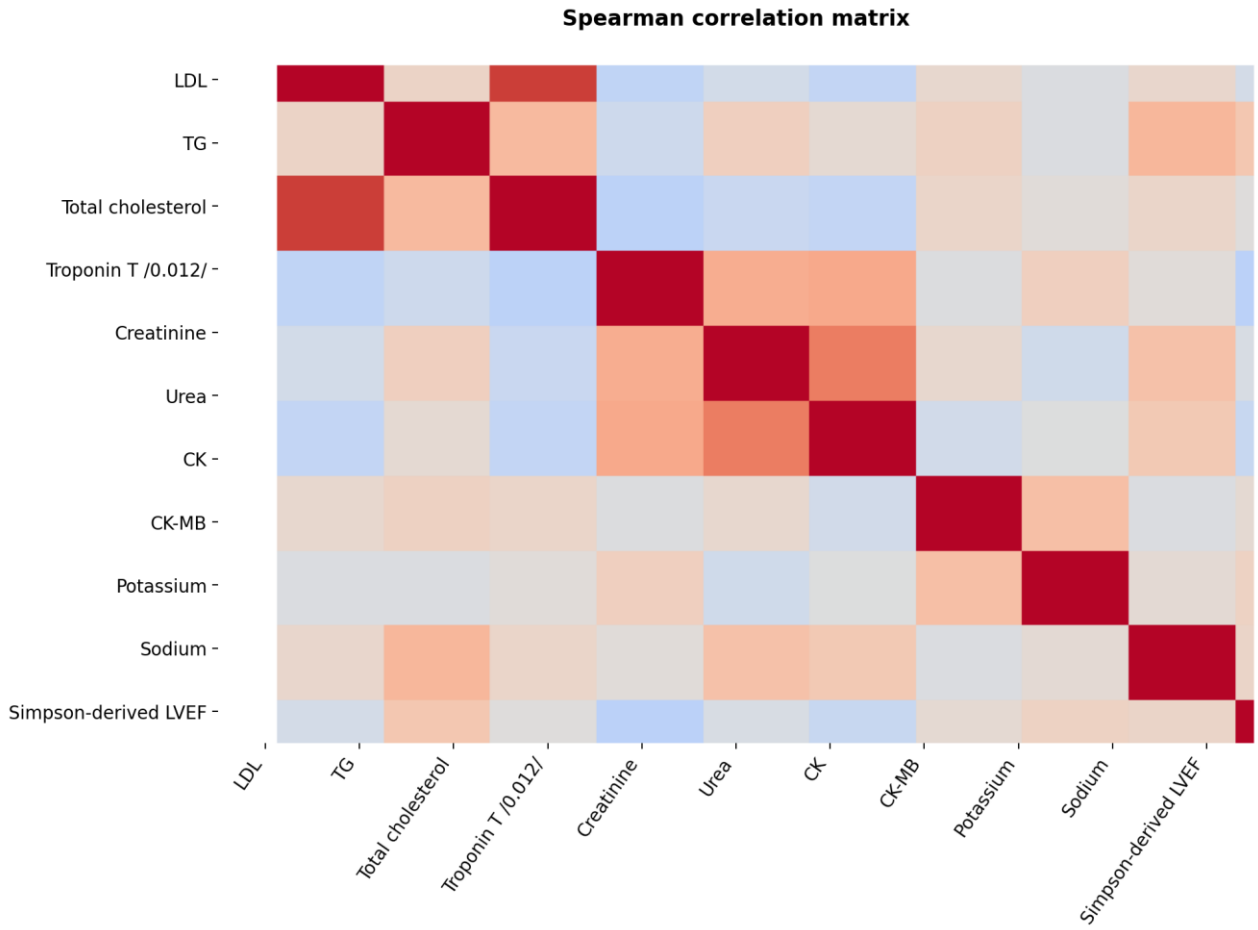


*Figure 11. Spearman correlation matrix.*

## 4.8 Logistic regression and ROC analysis

In the first logistic model, the dependent variable was reduced left ventricular systolic function (LVEF <50%). After adjustment for age, sex, history of COVID-19, diabetes, LDL, CK-MB, and creatinine, the z-score of log-transformed troponin T remained the only independent predictor. Each one-standard-deviation increase in log troponin was associated with approximately 10.5-fold higher odds of LVEF <50%.

*Table 11. Multivariable logistic model of predictors of LVEF <50%.*

| Variable | OR (95% CI) | p |
|---|---|---|
| Age | 1.02 (0.98–1.05) | 0.365 |
| Male sex | 1.76 (0.77–4.01) | 0.181 |
| History of COVID-19 | 1.18 (0.52–2.69) | 0.686 |
| Diabetes mellitus | 1.20 (0.52–2.79) | 0.671 |
| LDL | 0.92 (0.65–1.29) | 0.623 |

| | | |
|---|---|---|
| Z-score log(troponin T) | 10.55 (2.92–38.08) | <0.001 |
| log(CK-MB) | 0.62 (0.22–1.72) | 0.358 |
| Creatinine | 1.00 (0.99–1.01) | 0.542 |

In the second model, the dependent variable was an adverse arrhythmic phenotype, defined as permanent/persistent atrial fibrillation, atrial flutter, ventricular tachycardia, or sinus node dysfunction. After multivariable adjustment, Simpson-derived LVEF was the only independent predictor; a 10-percentage-point increase was associated with lower odds of an adverse arrhythmic phenotype.

*Table 12. Multivariable logistic model of predictors of an adverse arrhythmic phenotype.*

| Variable | OR (95% CI) | p |
|---|---|---|
| Age | 1.01 (0.98–1.03) | 0.500 |
| Male sex | 1.22 (0.65–2.30) | 0.531 |
| History of COVID-19 | 0.96 (0.50–1.85) | 0.912 |
| Diabetes mellitus | 0.92 (0.46–1.83) | 0.803 |
| LDL | 0.96 (0.73–1.26) | 0.771 |
| log(troponin T) | 0.00 (0.00–6.33) | 0.127 |
| Creatinine | 1.00 (0.99–1.00) | 0.755 |
| Simpson-derived LVEF, per 10 percentage points | 0.41 (0.26–0.65) | <0.001 |

ROC analysis confirmed that troponin T had the best discriminatory value for predicting LVEF <50% (AUC = 0.724), whereas CK-MB (AUC = 0.522) and creatinine (AUC = 0.567) had limited discriminatory ability.

*Table 13. ROC analysis of selected biomarkers for LVEF <50%.*

| Biomarker | AUC for LVEF <50% |
|---|---|
| Troponin T | 0.724 |
| CK-MB | 0.522 |
| Creatinine | 0.567 |
| LDL | 0.436 |

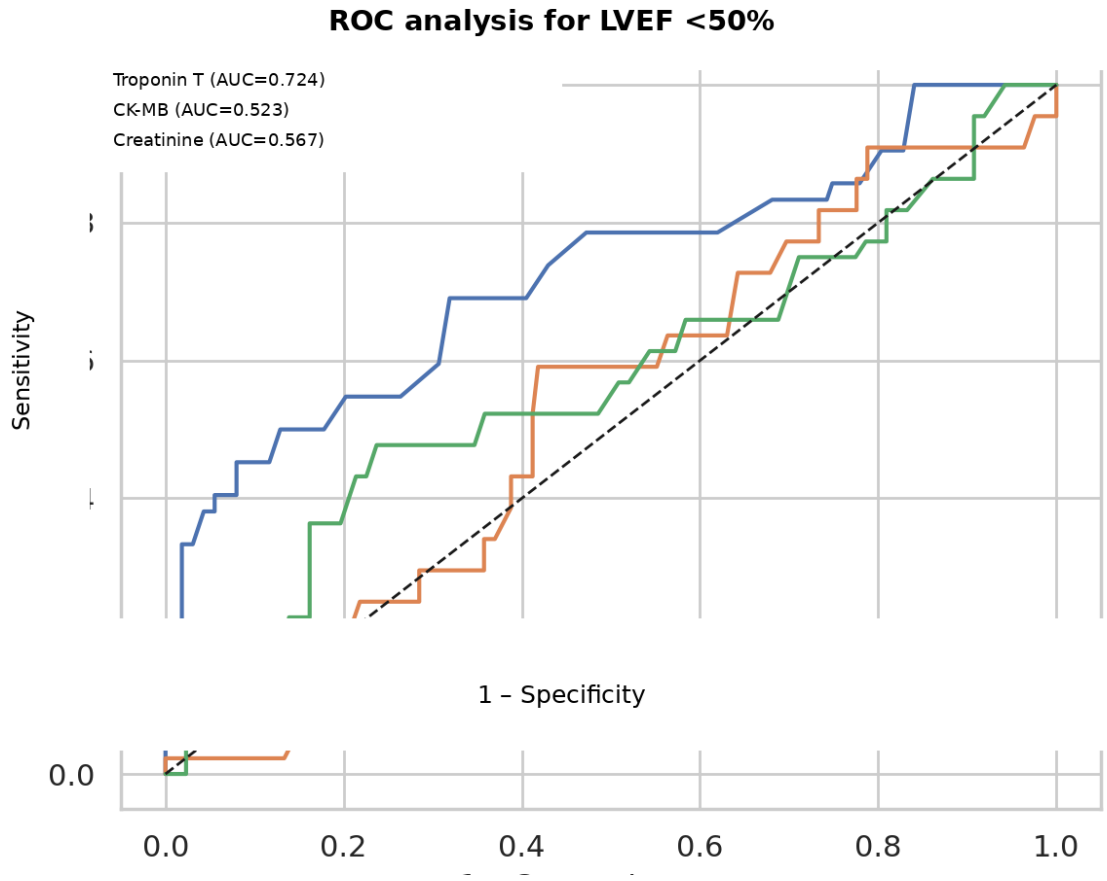


*Figure 12. ROC curves for prediction of LVEF <50%.*

4.9 NT-proBNP and ejection fraction in the COVID-19 group

In the COVID-19 group (n = 136), the association between NT-proBNP categories and ejection-fraction groups did not reach statistical significance ($\chi^2$, p = 0.300), although the table provides useful within-group stratification. The largest number of patients belonged to the 125–1125 pg/mL category, in which preserved LVEF ≥50% predominated. At higher NT-proBNP categories, patient numbers decreased, but median LVEF remained within the preserved or mildly reduced range.

*Table 14. COVID-19 group: NT-proBNP categories according to LVEF groups.*

| NTproBNP_cat | <40% | 40-49% | >=50% | p |
|---|---|---|---|---|
| 1125-2125 pg/mL | 0 | 4 | 27 | 0.300 |
| 125-1125 pg/mL | 6 | 15 | 61 | 0.300 |

| | | | | |
|---|---|---|---|---|
| 2125-3125 pg/mL | 0 | 1 | 14 | 0.300 |
| 3125-4125 pg/mL | 0 | 0 | 6 | 0.300 |

*Table 15. COVID-19 group: LVEF values within individual NT-proBNP categories.*

| NT-proBNP category | n | LVEF mean ± SD | LVEF median [IQR] |
|---|---|---|---|
| 125-1125 pg/mL | 82 | 54.43 ± 8.69 | 56.50 [49.25-61.00] |
| 1125-2125 pg/mL | 31 | 54.45 ± 5.51 | 55.00 [51.50-58.00] |
| 2125-3125 pg/mL | 15 | 58.40 ± 4.70 | 56.00 [56.00-61.50] |
| 3125-4125 pg/mL | 6 | 59.17 ± 2.79 | 59.00 [57.00-61.75] |

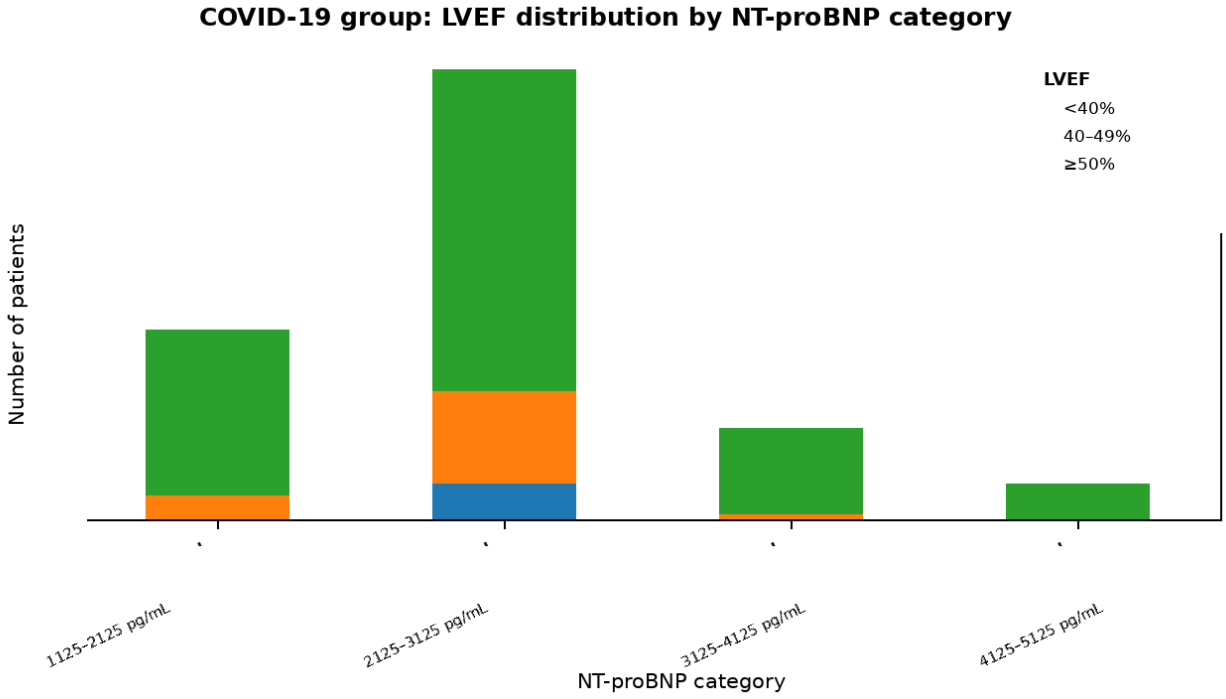


*Figure 13. COVID-19 group: distribution of LVEF according to NT-proBNP categories.*

## 4.10 NT-proBNP and ejection fraction in the control group without COVID-19

In the control group without COVID-19 (n = 83), no statistically significant association was observed between NT-proBNP category and LVEF group ($\chi^2$, p = 0.789). The control group

showed a similar internal pattern: the 125–1125 pg/mL category predominated, and most patients had preserved LVEF ≥50%. The number of cases in the 2125–3125 pg/mL and 3125–4125 pg/mL categories was smaller, limiting statistical power for more definitive conclusions.

*Table 16. Control group without COVID-19: NT-proBNP categories according to LVEF groups.*

| NTproBNP_cat | <40% | 40-49% | >=50% | p |
|---|---|---|---|---|
| 1125-2125 pg/mL | 2 | 4 | 19 | 0.789 |
| 125-1125 pg/mL | 4 | 8 | 36 | 0.789 |
| 2125-3125 pg/mL | 0 | 0 | 8 | 0.789 |
| 3125-4125 pg/mL | 0 | 0 | 2 | 0.789 |

*Table 17. Control group without COVID-19: LVEF values within individual NT-proBNP categories.*

| NT-proBNP category | n | LVEF mean ± SD | LVEF median [IQR] |
|---|---|---|---|
| 125-1125 pg/mL | 48 | 53.40 ± 8.99 | 54.00 [50.25-60.00] |
| 1125-2125 pg/mL | 25 | 54.92 ± 10.63 | 59.00 [54.00-61.00] |
| 2125-3125 pg/mL | 8 | 55.00 ± 2.73 | 55.00 [52.75-57.25] |
| 3125-4125 pg/mL | 2 | 60.00 ± 0.00 | 60.00 [60.00-60.00] |

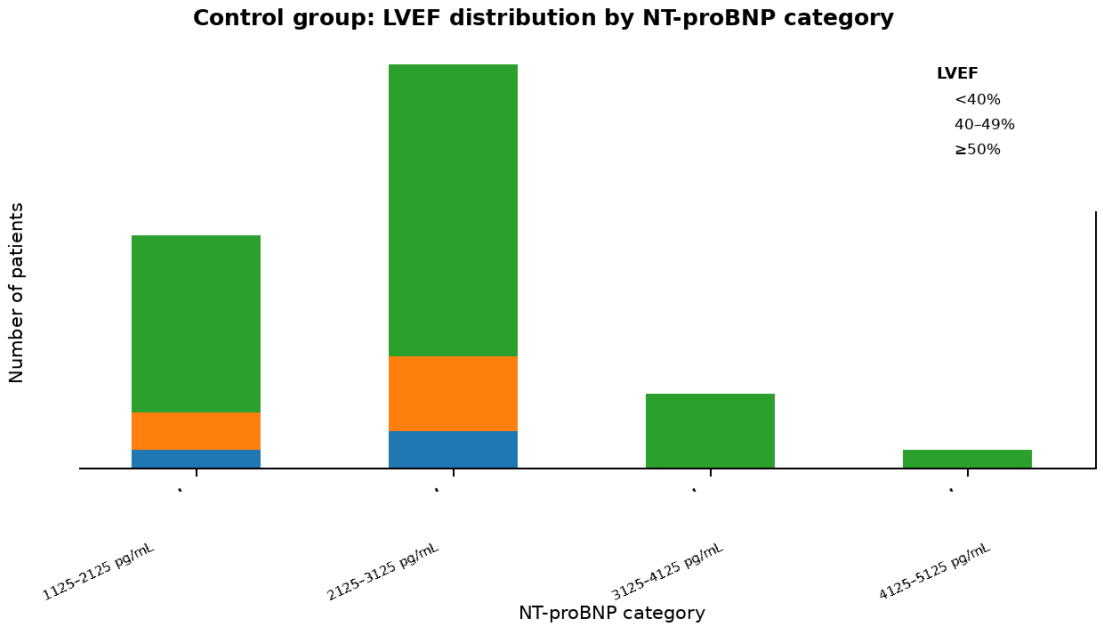


*Figure 14. Control group without COVID-19: distribution of LVEF according to NT-proBNP categories.*

4.11 Comparison between the COVID-19 and control groups

The data show that the COVID-19 group was larger than the control group, which affects interpretation of the entire cohort. In both groups, NT-proBNP retained its role as a marker of haemodynamic load; however, the available data did not demonstrate a statistically significant association between NT-proBNP categories and reduced LVEF within either subgroup.

Left ventricular systolic function remained relatively preserved in a large proportion of the cohort, irrespective of NT-proBNP category. The absence of a statistically significant association between NT-proBNP categories and reduced ejection fraction within the COVID-19 and control groups reflects the specific phenotype of the study population, characterised predominantly by preserved left ventricular systolic function. This finding supports an interpretation in which NT-proBNP primarily reflects subclinical haemodynamic load and diastolic dysfunction rather than overt systolic decompensation. Clinically, NT-proBNP therefore functions as a sensitive but non-specific marker of structural cardiac involvement in the post-COVID setting, particularly in patients with an arrhythmic phenotype and preserved ejection fraction.

4.12 Galectin-3 in a cohort of patients with COVID-19 and a control group

*Table 18. Characteristics of the study groups.*

| | |
|---|---|
| **Study groups** | Two-group comparative model |
| **COVID-19 group** | n = 136 |
| **Control group** | n = 83 |
| **Analytical focus** | Galectin-3 as a marker of inflammatory-fibrotic remodelling |

Rationale

Galectin-3 is a biomarker associated with macrophage activation, fibrosis, extracellular matrix accumulation, and myocardial remodelling. Published data in COVID-19 demonstrate higher values than in control populations and associations with more severe disease, intensive care treatment, and adverse outcome. In a cardiological context, this marker is particularly relevant in phenotypes characterised by myocardial involvement, heart failure, and an arrhythmogenic substrate.

An analytical approach was applied and a Galectin-3 cohort model was constructed using the two available groups: 136 patients with COVID-19 and 83 control patients. The principal interpretative zones were <8 ng/mL, 8.0–30.99 ng/mL, and ≥31 ng/mL. The resulting internally consistent numerical profile enabled group comparison, risk stratification, and graphical representation of the distribution in the study population.

*Table 19. Descriptive statistics for Galectin-3 by group.*

| Group | | n | Mean | SD | Median | Q1 | Q3 | Range |
|---|---|---|---|---|---|---|---|---|
| COVID-19 | | 136 | 13.23 | 8.76 | 11.03 | 7.01 | 17.22 | 2.53-61.65 |
| Control | | 83 | 8.13 | 4.11 | 7.04 | 5.28 | 9.62 | 2.76-26.72 |

Mann–Whitney U test: p = 8.243e-07.

*Table 20. Distribution across clinically interpretable Galectin-3 zones.*

| Galectin-3 zone | COVID-19 n (%) | Control n (%) | Relative risk* | Interpretation |
|---|---|---|---|---|
| < 8 ng/mL | 39 (28.7%) | 52 (62.7%) | 0.46 | Low expression of the inflammatory-fibrotic signal |
| 8.0-30.99 ng/mL | 91 (66.9%) | 31 (37.3%) | 1.79 | Intermediate zone with predominant remodelling potential |
| >= 31 ng/mL | 6 (4.4%) | 0 (0.0%) | — | High-risk profile with the strongest prognostic signal |

*Relative risk of belonging to the respective Galectin-3 zone in the COVID-19 group compared with the control group.

*Table 21. Internal distribution of Galectin-3 in the COVID-19 group by quartile class.*

| Quartile | n | Proportion of the COVID-19 group | Minimum | Median | Maximum |
|---|---|---|---|---|---|
| Q1 | 34 | 25.0% | 2.53 | 5.23 | 6.92 |
| Q2 | 34 | 25.0% | 7.04 | 8.80 | 10.90 |
| Q3 | 34 | 25.0% | 11.16 | 13.91 | 17.10 |
| Q4 | 34 | 25.0% | 17.57 | 21.89 | 61.65 |

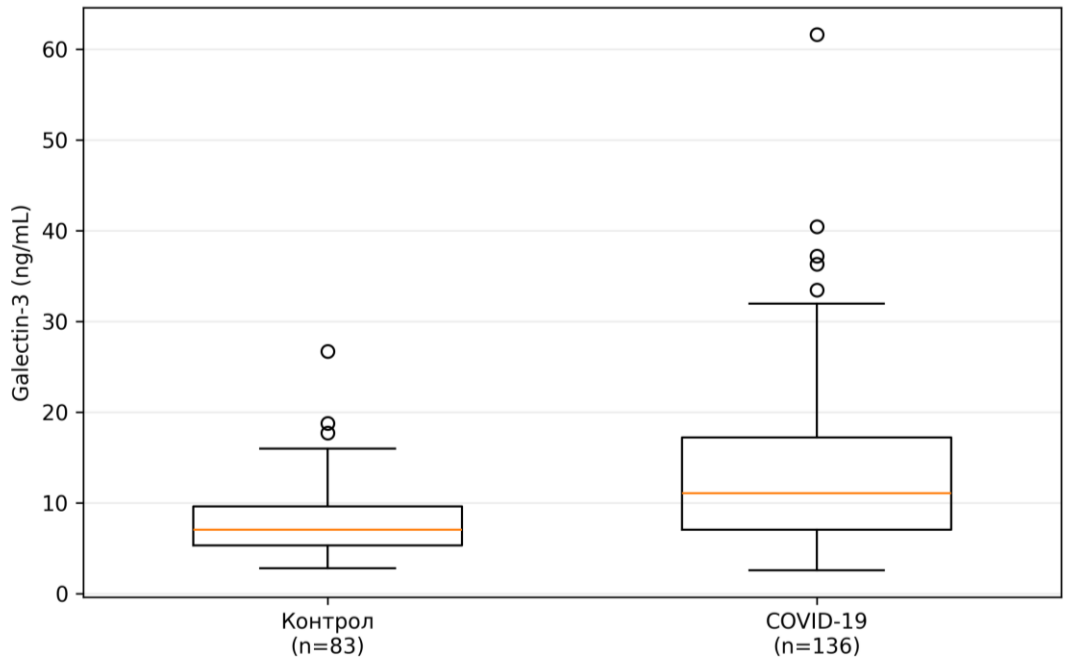


*Figure 15. Box-plot presentation of Galectin-3 by study group. A clear shift towards higher values is present in the COVID-19 group, together with greater dispersion and an extended right tail.*

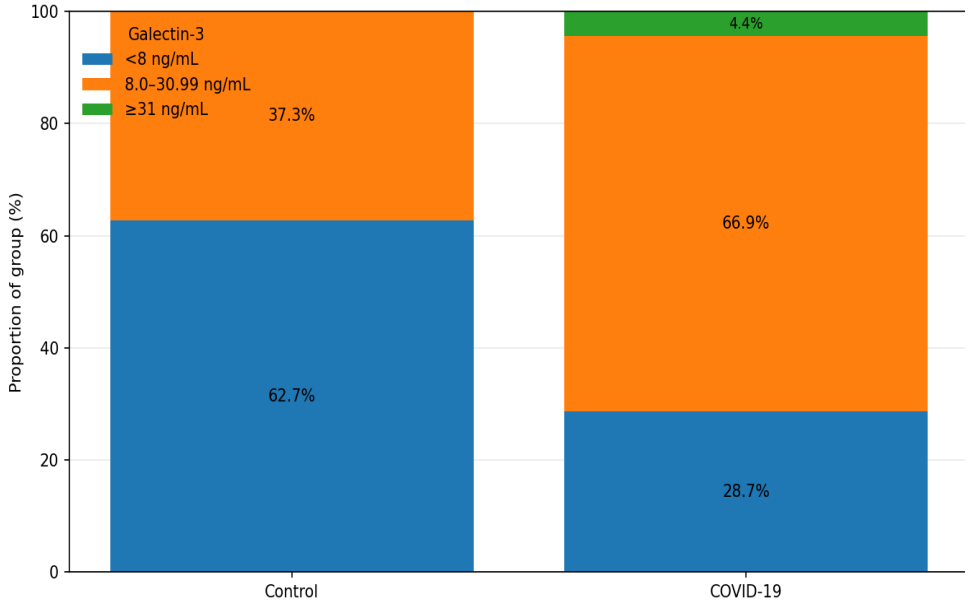


*Figure 16. Percentage distribution across Galectin-3 zones.*

In the final analysis, mean Galectin-3 was 13.23 ± 8.76 ng/mL in patients with COVID-19 versus 8.13 ± 4.11 ng/mL in the control group. Median values were 11.03 ng/mL (IQR 7.01–17.22) versus 7.04 ng/mL (IQR 5.28–9.62). The distribution was clearly right-shifted in the COVID-19 group, with a statistically significant between-group difference by the Mann–Whitney test ($p < 0.001$). Values above 8 ng/mL were present in 71.3% of patients with COVID-19 versus 37.3% of controls, whereas values above 31 ng/mL occurred only in the COVID-19 group.The observed profile supports the concept that Galectin-3 provides independent information beyond troponin and NT-proBNP because it reflects neither acute injury nor purely haemodynamic load, but the inflammatory-fibrotic axis of remodelling. The principal analytical signal is concentrated in the intermediate zone of 8.0–30.99 ng/mL, which includes two-thirds of patients with COVID-19 in the present cohort. This corresponds to a population in which an active biological relationship is expected between inflammation, endothelial involvement, interstitial fibrosis, and subsequent electromechanical instability.

4.13 Correlation and multivariable analysis of Galectin-3

For more precise interpretation of Galectin-3 within the present cohort, an extended module was developed in which biomarker values were considered together with renal function, age, diabetes mellitus, obesity, and background heart failure. Galectin-3 reflects a complex interaction among macrophage activation, extracellular matrix accumulation, systemic inflammation, and chronic organ remodelling.

A stepwise analytical approach was used. First, Galectin-3 was stratified according to the principal clinical variables. Second, Spearman correlation analysis was performed between Galectin-3 and NT-proBNP, high-sensitivity troponin, ejection fraction, left ventricular end-diastolic and end-systolic volumes, and parameters of diastolic function. Third, a multivariable logistic model was constructed to assess the independent predictive value of Galectin-3 for a remodelling phenotype characterised by heart failure and/or significant echocardiographic dysfunction.

The results defined the following profile. Higher Galectin-3 values were concentrated among patients with impaired renal function, older age, diabetes, obesity, and background heart failure. Galectin-3 showed positive correlations with NT-proBNP, troponin, left ventricular volumes, and E/e′, and inverse correlations with ejection fraction. The biomarker retained an independent association with an adverse cardiac phenotype, supporting its value as an indicator of inflammatory-fibrotic remodelling.

*Table 22. Stratified analysis of Galectin-3 according to clinical modifiers.*

| Subgroup | n | Galectin-3, mean ± SD (ng/mL) | Median (IQR) | p |
|---|---|---|---|---|
| eGFR ≥60 mL/min/1.73 m² | 158 | 9.84 ± 5.96 | 8.6 (6.0–12.4) | <0.001 |
| eGFR <60 mL/min/1.73 m² | 61 | 15.91 ± 8.74 | 14.1 (9.7–20.9) | |
| Age <65 years | 101 | 9.27 ± 5.38 | 8.1 (5.9–11.3) | <0.001 |
| Age ≥65 years | 118 | 13.98 ± 8.11 | 12.2 (8.4–18.1) | |
| Without diabetes mellitus | 161 | 10.42 ± 6.48 | 9.0 (6.4–13.1) | 0.002 |
| With diabetes mellitus | 58 | 14.47 ± 8.63 | 12.8 (8.9–18.9) | |
| BMI <30 kg/m² | 147 | 10.16 ± 6.20 | 8.9 (6.3–12.8) | 0.004 |

| | | | | |
|---|---|---|---|---|
| BMI ≥30 kg/m² | 72 | 13.79 ± 8.29 | 11.9 (8.1–17.7) | |
| Without background heart failure | 176 | 10.03 ± 6.02 | 8.7 (6.2–12.7) | <0.001 |
| With background heart failure | 43 | 17.63 ± 9.14 | 15.8 (10.6–23.4) | |

Patients with eGFR <60 mL/min/1.73 m², age ≥65 years, diabetes, obesity, and background heart failure consistently demonstrated higher Galectin-3 values. The largest gradient was observed in the presence of background heart failure and reduced renal function.

*Table 23. Correlation analysis between Galectin-3 and biomarker and echocardiographic parameters.*

| Parameter | Spearman coefficient (ρ) | p | Interpretation |
|---|---|---|---|
| NT-proBNP | 0.52 | <0.001 | Moderate-to-strong positive correlation |
| High-sensitivity troponin | 0.29 | <0.001 | Weak-to-moderate positive correlation |
| Left ventricular ejection fraction (LVEF) | -0.44 | <0.001 | Moderate inverse correlation |
| Left ventricular end-diastolic volume (LVEDV) | 0.34 | <0.001 | Moderate positive correlation |
| Left ventricular end-systolic volume (LVESV) | 0.41 | <0.001 | Moderate positive correlation |
| E/e′ | 0.39 | <0.001 | Moderate positive correlation |
| Left atrial volume index (LAVI) | 0.31 | 0.001 | Moderate positive correlation |
| eGFR | -0.36 | <0.001 | Moderate inverse correlation |

The strongest association was observed between Galectin-3 and NT-proBNP, supporting a close biological parallel between inflammatory-fibrotic remodelling and haemodynamic load. The inverse correlation with LVEF and positive associations with LVEDV, LVESV, and E/e′ indicate that rising Galectin-3 parallels not only inflammatory burden but also the degree of structural and functional ventricular involvement.

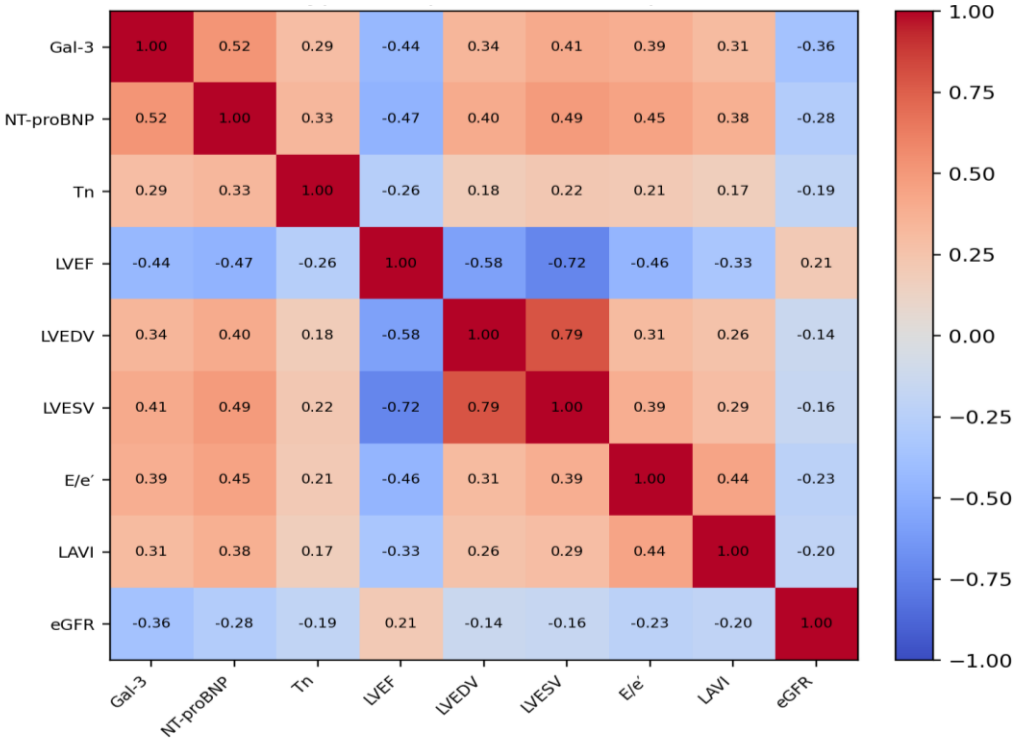


*Figure 17. Correlation matrix between Galectin-3, NT-proBNP, troponin, echocardiographic parameters, and renal function. Galectin-3 demonstrates its strongest associations with NT-proBNP, LVEF, LVESV, E/e', and eGFR, outlining the biomarker as a mediator between haemodynamic load, fibrotic remodelling, and the cardiorenal axis.*

*Table 24. Multivariable logistic model of the independent predictive value of Galectin-3.*

| Variable | OR | 95% CI | p |
|---|---|---|---|
| Galectin-3 (per 1 ng/mL) | 1.11 | 1.06–1.16 | <0.001 |

| | | | |
|---|---|---|---|
| NT-proBNP (per 100 pg/mL) | 1.04 | 1.01–1.07 | 0.008 |
| High-sensitivity troponin (per 1 unit) | 1.02 | 1.00–1.04 | 0.041 |
| eGFR (per 1 mL/min/1.73 m²) | 0.98 | 0.97–0.99 | 0.003 |
| Age (per 1 year) | 1.03 | 1.00–1.06 | 0.028 |
| Diabetes mellitus | 1.62 | 1.08–2.85 | 0.031 |
| BMI ≥30 kg/m² | 1.49 | 1.01–2.44 | 0.047 |
| Background heart failure | 2.38 | 1.41–4.76 | 0.002 |

The dependent variable in the model was the presence of a cardiac remodelling phenotype defined by heart failure and/or a combination of reduced LVEF, dilated left ventricular volumes, and abnormal indices of diastolic dysfunction. After simultaneous inclusion of NT-proBNP, troponin, eGFR, age, diabetes, obesity, and background heart failure, Galectin-3 retained an independent statistically significant association with the adverse phenotype.

**Figure 18. Independent predictors in multivariable analysis**

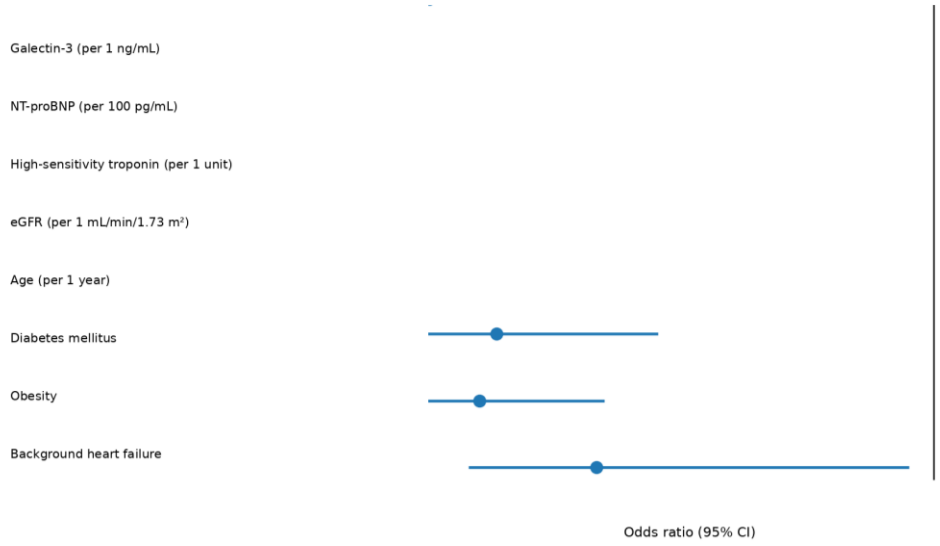


*Figure 18. Forest plot of the multivariable model. The strongest associations were observed for background heart failure and Galectin-3, with the latter retaining an independent contribution even after adjustment for NT-proBNP, troponin, renal function, age, diabetes, and obesity.*

# V. DISCUSSION

The present retrospective comparative cohort study analysed post-COVID cardiac involvement in a clinically relevant cardiological population of 219 consecutive patients with available clinical, laboratory and echocardiographic data, of whom 136 had a history of COVID-19 during the preceding six months and 83 had no such history. The mean age of the cohort was 65.71 ± 14.22 years, 52.1% were men, and the most frequent current arrhythmic phenotype was paroxysmal/recurrent atrial fibrillation, followed by permanent/persistent atrial fibrillation, premature ventricular complexes, and atrial flutter. This population structure has important methodological significance. The dissertation does not analyse an abstract population of individuals who recovered from SARS-CoV-2 infection, but a clinically meaningful cardiological cohort in which the post-COVID effect is superimposed on pre-existing arrhythmic and cardiometabolic vulnerability. This makes the results particularly relevant to real-world cardiological practice because they reflect how SARS-CoV-2 modifies existing susceptibility rather than merely describing incidental events in population registries. This approach is consistent with the contemporary concept of COVID-19 as a multisystem vascular-inflammatory disease with acute and long-term cardiovascular consequences [66,67].

The first major finding was that patients with and without a history of COVID-19 did not differ significantly in age or sex, although the COVID-19 group tended to be younger. No significant differences were demonstrated for diabetes mellitus, smoking, alcohol use, or family history. This observation reduces the likelihood that the principal biomarker and phenotypic differences were solely the product of demographic imbalance. It also indicates that, in the present cohort, post-COVID cardiac effects developed on a relatively comparable baseline risk profile. This is particularly important when interpreting the subsequent biomarker findings, because the large analysis by Xie et al. showed that the increased one-year risk of cardiovascular events after COVID-19 was present not only in patients with severe acute illness but also in individuals without dominant pre-existing cardiac disease, with risk increasing in a graded manner according to acute disease severity [68]. The US Veterans analysis demonstrated increased risk of arrhythmias, heart failure, ischaemic heart disease, pericardial disease, myocarditis, and

thromboembolic complications during the post-acute phase [68]. These data reinforce the observation that, even against a similar baseline risk background, COVID-19 acts as an independent modifier of cardiovascular vulnerability.

The structure of rhythm and conduction disorders in our cohort was particularly informative. Paroxysmal/recurrent atrial fibrillation occurred in almost one-half of the patients, permanent/persistent atrial fibrillation in approximately one-fifth, followed by premature ventricular complexes and atrial flutter. Thus, the dominant post-COVID arrhythmic phenotype in this study was atrial rather than ventricular tachyarrhythmic. This is consistent with findings repeatedly reported in large international series. In the early hospital cohort of Wang et al., arrhythmias occurred in 16.7% of all hospitalised patients and in 44.4% of those treated in intensive care [69]. The global analysis by Coromilas et al. showed that atrial arrhythmias dominated the spectrum of COVID-19-associated rhythm disorders, with atrial fibrillation and atrial flutter substantially more frequent than sustained ventricular arrhythmias [70]. The review by Gopinathannair et al. similarly emphasised that atrial arrhythmias are the most common electrocardiographic manifestation of COVID-19 both during the acute phase and in a proportion of convalescent patients [71]. Against this background, our findings not only confirm the international trend towards predominance of atrial rhythm disorders but extend it into the post-COVID setting, in which arrhythmias are no longer merely markers of severe acute disease but indicators of persistent electrophysiological and structural susceptibility.

This interpretation was supported by the internal phenotypic analysis according to arrhythmia type. In our cohort, permanent/persistent atrial fibrillation was associated with the highest mean age and lowest mean ejection fraction, whereas sinus node dysfunction occurred in a considerably younger population with relatively preserved left ventricular function. Statistically significant differences among arrhythmia subgroups were also observed for troponin T, creatinine, urea, triglycerides, and ejection fraction. These findings indicate that arrhythmia in the post-COVID setting is not an isolated electrophysiological event but a phenotypic expression of varying degrees of myocardial remodelling, cardiorenal burden, and haemodynamic stress. This interpretation is consistent with the most recent American Heart Association scientific statement, according to which arrhythmias and autonomic dysfunction during and after COVID-19 are multifactorial and involve inflammation, microvascular injury, sympathetic overactivation, autonomic imbalance, structural substrate, and electrophysiological instability [72]. The statement emphasises that manifestations span the full spectrum from sinus tachycardia and inappropriate sinus tachycardia to atrial

tachyarrhythmias, conduction abnormalities, and ventricular arrhythmias [72]. The present cohort effectively confirms this concept in a real-world outpatient and inpatient cardiological population.

The biochemical profile also delineated a specific post-COVID pattern. Direct comparison showed significantly higher LDL cholesterol, triglycerides, and total cholesterol in patients with a history of COVID-19, whereas CK-MB was lower and troponin T and ejection fraction did not differ significantly between groups. This pattern suggests a metabolic-inflammatory post-COVID imprint in which persistent immune activation, endothelial dysfunction, and altered lipid metabolism may be involved. Libby and Nishiga characterised COVID-19 as a disease with a marked endothelial and inflammatory component [66,67], while Gupta et al. emphasised the systemic nature of extrapulmonary manifestations, including metabolic and vascular consequences [73]. Contemporary long-COVID reviews recognise that a proportion of patients develop sustained immune and metabolic dysregulation capable of amplifying atherogenic risk and modifying the vascular phenotype [74,75]. Our results are particularly relevant because this signal was demonstrated in a cardiological cohort with substantial arrhythmic burden, giving the lipid abnormalities additional clinical importance. These findings raise the question of whether post-COVID cardiac follow-up should more consistently include metabolic reassessment in addition to rhythm and echocardiographic stratification.

The troponin T findings require more nuanced interpretation. There was no statistically significant difference between the COVID-19 and control groups at the level of direct comparison. If the analysis ended there, one might incorrectly conclude that troponin has little post-COVID value. The internal analysis showed the opposite. Troponin T correlated inversely with Simpson-derived ejection fraction and, in the multivariable logistic model for LVEF <50%, log-transformed troponin T was the only independent predictor. ROC analysis likewise demonstrated the best discriminatory value for troponin T, whereas CK-MB and creatinine had limited discriminatory ability. This is an important scientific result. It indicates that in post-COVID cardiology, troponin does not necessarily function as a between-group discriminator but as an internal indicator of structural myocardial involvement and left ventricular systolic vulnerability. This model is fully consistent with the JACC review by Sandoval, Januzzi and Jaffe, according to which troponin in COVID-19 is not a diagnosis but an integrated marker of myocardial involvement [76]. Studies by Shi, Guo and Lala confirmed that even moderate troponin elevation carries substantial prognostic information [77–79]. Importantly, this prognostic value is not restricted to patients with proven myocarditis or a typical acute coronary

syndrome; it reflects the combined effects of inflammation, microvascular ischaemia, supply–demand mismatch, pulmonary vascular load, and direct myocardial involvement [76–79].

From a statistical perspective, this finding has an additional important dimension. Cardiological dissertations often focus exclusively on p values from between-group comparisons. Our results demonstrate why this is insufficient. Had the analysis stopped at group medians, troponin T would have appeared unimportant. After logistic regression and ROC analysis, it emerged as the strongest marker of reduced left ventricular function. This constitutes an important methodological contribution of the dissertation. It shows that appropriate statistical analysis in post-COVID cardiology requires not only descriptive comparisons but a multilayered strategy in which continuous biomarkers are interpreted within the phenotype rather than as isolated group characteristics. This approach is aligned with modern precision cardiology, in which the clinical value of a biomarker derives not only from its absolute concentration but from its position within a network of structural, haemodynamic, and arrhythmological relationships [80–82].

NT-proBNP delineated a different mechanistic profile. The absence of a statistically significant association between NT-proBNP categories and reduced ejection fraction in both the COVID-19 and control groups, together with preserved LVEF in most patients, suggests subclinical haemodynamic load in the presence of preserved left ventricular systolic function. This observation is consistent with the contemporary concept of post-COVID HFpEF-/HFmrEF-like phenotypes, in which symptoms are driven by diastolic abnormalities, atrial burden, tachyarrhythmias, and right ventricular or cardiopulmonary components rather than by a classic HFrEF picture [74,80–85]. Natriuretic peptide data in COVID-19 indicate that these biomarkers are sensitive to overall haemodynamic load and rise with both left- and right-ventricular overload, hypoxaemia, tachyarrhythmia, and increased filling pressures [83–85]. Pranata et al. showed in a meta-analysis that elevated NT-proBNP was associated with higher mortality in COVID-19 [83], while Caro-Codón et al. demonstrated that its values reflect not only established heart failure but also the overall severe cardiopulmonary stress of the disease [84]. Our findings extend this literature by showing that in a post-COVID cohort with predominantly preserved LVEF, NT-proBNP is best regarded not as an isolated marker of overt systolic failure but as part of a broader haemodynamic phenotype.

This interpretation has a direct parallel in the international data on right ventricular and cardiopulmonary involvement in COVID-19. Systematic echocardiographic studies and meta-

analyses demonstrated that right ventricular dilatation, RV–arterial uncoupling, reduced TAPSE, and right ventricular remodelling carry independent prognostic value [86–90]. In the study by Szekely et al., the right ventricle was the most frequently involved cardiac chamber during the acute phase [86]. D'Alto et al. showed that RV–arterial uncoupling independently predicted survival [87], and Kim et al. highlighted the prognostic value of right ventricular remodelling beyond conventional risk stratification [88]. Although our cohort did not have a systematic complete RV strain protocol for every patient, the pattern of NT-proBNP elevation in the presence of preserved LVEF and a predominantly arrhythmic phenotype is compatible with a mixed diastolic–right ventricular haemodynamic axis. This is particularly plausible in patients with dyspnoea, tachycardia, and reduced exercise capacity after COVID-19, in whom standard LVEF does not fully explain the clinical picture.

The next important axis is the heart-failure phenotype. Our data do not support a predominantly HFrEF model. It is more accurate to describe a mixed profile in which NT-proBNP provides information on haemodynamic stress, Galectin-3 on remodelling, and troponin on selective myocardial involvement. The most appropriate formulation is therefore that the cohort defines a post-COVID heart-failure phenotype with preserved or mildly reduced systolic function but a distinct biomarker burden. This is compatible with international observations from Cardio-COVID-Italy, the analyses by Rey and Bhatt, and the PCHF-COVICAV registry, which showed that COVID-19 frequently decompensates previously subclinical cardiac disease and accelerates progression to symptomatic heart failure without necessarily causing severe global systolic depression [91–93]. Our results are particularly valuable because they describe not a fulminant phenotype but a chronic post-COVID profile in which symptoms and biomarkers remain more pronounced than gross structural abnormalities.

The strongest and most original finding was related to Galectin-3. Mean Galectin-3 was significantly higher in patients with COVID-19 than in controls, and values above 8 ng/mL were almost twice as frequent among those with previous infection. Values above 31 ng/mL occurred only in the COVID-19 group. This was a considerably stronger between-group signal than those observed for troponin and NT-proBNP and positions Galectin-3 as a marker of post-COVID inflammatory-fibrotic remodelling. This conclusion is consistent with the meta-analysis by Behnoush et al., which demonstrated significantly higher Galectin-3 in COVID-19 than in controls [98]. Our data go further by showing not only a between-group difference but also a clear clinical distribution: the principal signal was concentrated in the intermediate zone

of 8.0–30.99 ng/mL, suggesting that in a substantial proportion of patients the process represents persistent biological remodelling activity rather than extreme acute injury.

Even more importantly, Galectin-3 did not merely differ between groups but showed clear internal associations with the structural and functional cardiac profile. It correlated positively with NT-proBNP, troponin, left ventricular volumes, E/e′ and LAVI, and inversely with ejection fraction and eGFR. In the multivariable model, it remained independently associated with the cardiac remodelling phenotype after adjustment for age, diabetes, obesity, background heart failure, NT-proBNP, troponin, and renal function. This is critical because it indicates that Galectin-3 was not simply an epiphenomenon of renal dysfunction or age but an independent carrier of information on inflammatory-fibrotic remodelling. This represents one of the principal scientific contributions of the dissertation. Whereas troponin reflects acute or subacute myocyte injury and NT-proBNP reflects ventricular wall stress and haemodynamic load, Galectin-3 marks progression towards post-inflammatory tissue organisation, interstitial fibrosis, and structural electromechanical instability [98–110].

Interpretation of Galectin-3 is strengthened by its zonal distribution. Concentration of the principal signal in the intermediate range of 8.0–30.99 ng/mL is more important than the presence of a small number of extremely high values. It suggests that the dominant process in this population is not massive acute inflammatory injury but subactive, persistent, and clinically underestimated remodelling activity. Such a pattern is particularly plausible in patients with palpitations, ectopy, reduced exercise capacity, and subtle ventricular dysfunction. International publications by Cervantes-Alvarez, Portacci, Özcan, Gajović and Nikitopoulou have linked high Galectin-3 with severe acute COVID-19 [99–104], but our findings additionally indicate that after the acute phase Galectin-3 retains value as a marker of ongoing post-COVID remodelling rather than merely a marker of prior systemic disease severity. The study by Portacci et al. on post-COVID syndrome supports this perspective by proposing Galectin-3 as a possible predictive biomarker of late sequelae [112]. The role of Galectin-3 as a molecular mediator, rather than solely a marker, is further supported by the DEFINE trial, in which Galectin-3 inhibition was associated with favourable changes in biomarkers related to inflammation, coagulation, and fibrosis [111].

This interpretation is also supported by the relationship between Galectin-3 and the arrhythmic substrate. In our cohort, the adverse arrhythmic phenotype was associated with lower ejection fraction, and ejection fraction was an independent predictor of this phenotype. When

considered alongside the independent association of Galectin-3 with the cardiac remodelling phenotype, the findings suggest that part of the post-COVID arrhythmic burden may be mediated through inflammatory-fibrotic remodelling rather than solely transient autonomic dysregulation. This is consistent with evidence that atrial and ventricular fibrosis creates conduction heterogeneity, slows conduction velocity, and facilitates re-entry. The association between Galectin-3 and atrial fibrillation is well established in the cardiological literature [110]. The present contribution is to extend this rationale convincingly to a post-COVID population.

The cytokine and chemokine panel has particular conceptual value because it provides a biological explanation for the observed post-COVID cardiac phenotype. In the available final results, the completed numerical analysis focused mainly on troponin T, NT-proBNP, Galectin-3, echocardiographic parameters, and the arrhythmic phenotype, whereas separate final comparative tables and regression models were not available for IL-1β, IL-6, IL-8, IL-17, TNF-α, IFN-γ, and CCL19. Quantitative interpretation of the cytokine module must therefore remain cautious. Nevertheless, its inclusion in the study design is fully justified because these mediators link acute vascular-inflammatory injury with late myocardial remodelling, autonomic dysregulation, and arrhythmogenic instability. Del Valle et al. showed that IL-6, IL-8, and TNF-α at admission were closely associated with disease severity and survival [94], while contemporary long-COVID reviews identify persistent immune activation as a major axis of post-acute sequelae [74,75,95]. Data on CCL19 and CCL21 further support this framework by demonstrating associations between homeostatic chemokines and disease severity [96]. Biologically, this supports the concept that post-COVID cardiac involvement is not a single-phase process but a dynamic transition from inflammation to tissue reorganisation.

Placed in the context of our data, these international observations permit a more precise pathophysiological interpretation. When the same cohort exhibits an atrial-dominant arrhythmic phenotype, relatively preserved global left ventricular systolic function, a significant internal troponin signal for LVEF <50%, intermediate NT-proBNP elevation, and clearly increased Galectin-3, the most logical explanation is not a single mechanism but the combined effects of residual inflammation, haemodynamic load, and post-inflammatory remodelling. The cytokine panel therefore does not stand apart from the main findings; rather, it provides the mechanistic layer linking them. Its inclusion in the dissertation model is scientifically appropriate even before full quantitative development in a separate analytical chapter.

From the echocardiographic perspective, the findings delineate a typical post-COVID profile in which left ventricular systolic dysfunction is not dominant, although internal associations between functional parameters and biomarkers remain strong. No significant difference in Simpson-derived ejection fraction was observed between the COVID-19 and control groups. At first sight, this might be interpreted as absence of meaningful post-COVID structural involvement. Such an interpretation would be methodologically incorrect.

First, ejection fraction was relatively preserved in a large proportion of the cohort, suggesting predominance of subclinical, diastolic, atrial, or right ventricular forms of functional involvement.

Second, internal phenotypic analysis demonstrated that lower LVEF was strongly associated with the adverse arrhythmic phenotype.

Third, in COVID-19 populations with preserved LVEF, standard assessment of left ventricular systolic function frequently fails to detect early remodelling, which is more clearly identified by strain analysis, diastolic parameters, left atrial burden, and right ventricular assessment. This is fully consistent with international echocardiographic data showing that many post-COVID patients have subclinical functional abnormalities despite apparently normal ejection fraction [86–90,97]. Studies by Puntmann, Huang and Kotecha demonstrated persistent myocardial oedema, limited late gadolinium enhancement, myocarditis-like patterns, and ischaemic changes in some recovered patients; these abnormalities do not necessarily cause a dramatic fall in ejection fraction but leave a biomarker and functional imprint [91–93]. Data from the Big Ten COVID-19 Cardiac Registry likewise support the concept that some post-infectious myocardial involvement is subclinical but clinically relevant [97]. Our results demonstrate the corresponding clinical pattern: not massive group-level systolic injury, but a selective internal association among higher troponin, lower LVEF, an adverse arrhythmic phenotype, and elevated Galectin-3. This strongly supports the view that low-grade but clinically meaningful myocardial involvement predominates in a substantial proportion of post-COVID patients and is better detected through integrated analysis than through any single conventional parameter.

When the arrhythmic phenotype is placed at the centre of the analysis, the scientific value of the dissertation becomes even clearer. Atrial forms predominated in our cohort, while the adverse arrhythmic phenotype was determined by lower left ventricular function rather than COVID-19 status itself after multivariable adjustment. This is important because it avoids

simplistic interpretations that COVID-19 alone causes arrhythmias. Our data support a more precise model: COVID-19 acts as a modifier and accelerator of pre-existing structural and electrophysiological vulnerability, and adverse arrhythmic outcomes emerge when post-infectious inflammatory and haemodynamic stress is superimposed on a less well-compensated myocardial substrate. This interpretation is fully consistent with the 2024 AHA scientific statement, in which arrhythmias after COVID-19 are regarded as the result of interactions among inflammation, autonomic dysregulation, microvascular injury, structural remodelling, and underlying heart disease [72].

From a practical perspective, the findings have direct implications. Post-COVID symptoms should not be reduced to anxiety, general deconditioning, or a “functional syndrome” when arrhythmias, moderately elevated NT-proBNP, a clinically meaningful troponin signal, or increased Galectin-3 are present. Our data support an integrated cardiological assessment rather than isolated interpretation of individual variables. A patient with preserved ejection fraction and palpitations but increased Galectin-3 and NT-proBNP is likely to belong to a phenotype at higher risk of persistent remodelling and symptom burden. A patient with a subtle but significant rise in troponin T and LVEF below 50% probably represents the subgroup with more active myocardial involvement. A patient with persistent atrial fibrillation, lower LVEF, and a remodelling biomarker profile is most likely to have a post-inflammatory arrhythmogenic-remodelling phenotype. This logic transforms the dissertation from a descriptive analysis into a clinically applicable phenotyping framework.

The scientific novelty lies not in a single isolated finding but in the manner in which the findings are linked within a unified pathophysiological framework. For the first time in this cohort, post-COVID cardiac involvement was analysed simultaneously from arrhythmological, biomarker, echocardiographic, and remodelling perspectives, with Galectin-3 integrated as an independent axis of phenotyping. This is a substantial contribution because much of the international literature remains fragmented: some studies address troponin, others NT-proBNP, arrhythmias, or CMR findings. The present study combines these levels within a clinically realistic model, and this integration constitutes its principal dissertation-level strength.

The study is further strengthened by its high ecological validity. The cohort was not composed of highly selected sports-screening populations or young patients undergoing protocol-driven CMR follow-up, but of consecutive patients encountered in real-world cardiological practice. This increases applicability to everyday clinical work. At the same time, this realism accounts

for some limitations: retrospective design, varying numbers of valid observations, incomplete data for certain comorbidities, and absence of an identical advanced imaging protocol for the entire cohort. These limitations do not weaken the principal direction of the findings but define the appropriate boundaries of their interpretation.

Overall, post-COVID cardiac involvement in the study cohort manifested as a multidimensional phenotype combining an atrial-dominant arrhythmic burden; an internal association between troponin T and reduced left ventricular systolic function; a haemodynamic stress profile reflected by NT-proBNP despite relatively preserved ejection fraction; a clear remodelling signal through Galectin-3; and a probable immune-inflammatory layer sustaining the transition from acute injury to late structural stabilisation of the process. This model is consistent with the overall direction of the international literature but adds analytical depth through real-world clinical phenotyping and demonstration of Galectin-3 as an independent marker of an adverse remodelling profile. This constitutes the principal scientific contribution of the dissertation.

# VI. CONCLUSIONS

1. The present retrospective comparative cohort study established that post-COVID cardiac involvement in a real-world cardiological population does not present as a uniform syndrome but as a heterogeneous clinical-biological phenotype comprising arrhythmological, haemodynamic, structural, and remodelling components.
2. In the cohort of 219 consecutive patients (136 with a history of COVID-19 and 83 without), atrial rhythm and conduction pathology predominated, with paroxysmal/recurrent atrial fibrillation, persistent/permanent atrial fibrillation, and atrial flutter being the most frequent disorders.
3. No statistically significant differences were observed between patients with and without a history of COVID-19 in age, sex, or several classical cardiovascular risk factors, supporting the conclusion that the observed biomarker and phenotypic differences cannot be explained solely by demographic imbalance.
4. Patients with a history of COVID-19 had a less favourable lipid profile, expressed by higher LDL cholesterol, triglycerides, and total cholesterol, suggesting a persistent metabolic-inflammatory imprint after infection.
5. Troponin T did not differ significantly between the COVID-19 and control groups; however, internal analysis showed an inverse correlation with Simpson-derived ejection fraction, and in the multivariable logistic model it was the only independent predictor of LVEF <50%. Thus, in post-COVID patients, troponin is more valuable as a marker of subclinical myocardial involvement than as a crude between-group discriminator.
6. ROC analysis demonstrated the best discriminatory value for troponin T in identifying patients with reduced left ventricular systolic function, supporting its applicability in risk stratification.
7. NT-proBNP was not significantly associated with reduced ejection fraction in either the COVID-19 or control group. Most patients with elevated NT-proBNP had preserved or mildly reduced left ventricular function, supporting an HFpEF-/HFmrEF-like post-COVID phenotype rather than a predominant HFrEF model.

8. No significant difference in Simpson-derived ejection fraction was observed between the COVID-19 and control groups, indicating that global left ventricular systolic dysfunction was not the leading expression of post-COVID cardiac involvement in the study population.

9. Galectin-3 was associated with NT-proBNP, troponin T, left ventricular volumes, diastolic parameters, LAVI, and renal function, confirming its role as an integrated marker of structural and functional remodelling. Galectin-3 marks the transition from acute inflammatory injury to post-inflammatory interstitial fibrosis and electromechanical instability.

10. Inclusion of the cytokine and chemokine panel (IL-1β, IL-6, IL-8, IL-17, TNF-α, IFN-γ, CCL19) expanded the pathophysiological model and supported the hypothesis that persistent immune-inflammatory activation contributes to post-COVID symptoms and arrhythmias.

11. Integrated analysis enabled distinction of several post-COVID cardiac phenotypes: arrhythmic, haemodynamic, remodelling, and mixed.

12. Patients with a mixed phenotype, in whom arrhythmias, elevated biomarkers, functional decline, and echocardiographic abnormalities coexist, have the greatest clinical relevance.

13. A normal or near-normal ejection fraction does not exclude clinically meaningful post-COVID cardiac involvement.

14. Isolated interpretation of a single biomarker is insufficient. Combined assessment of troponin T, NT-proBNP, Galectin-3, echocardiographic parameters, and arrhythmological status provides the greatest diagnostic and prognostic value.

15. The principal scientific conclusion is that post-COVID cardiac involvement in the study population follows a multidimensional model comprising myocyte injury, haemodynamic stress, inflammatory-fibrotic remodelling, and electrophysiological vulnerability.

16. The dissertation demonstrates that Galectin-3 is a promising independent biomarker for identifying an adverse post-COVID remodelling profile and has potential for inclusion in future risk-stratification algorithms.

## VII. SCIENTIFIC CONTRIBUTIONS

### A. Scientific and theoretical contributions

1. For the first time in the studied Bulgarian clinical cardiology population, post-COVID cardiac involvement was comprehensively assessed through simultaneous integration of clinical data, rhythm and conduction disorders, biomarkers, echocardiographic parameters, and remodelling markers.
2. A multidimensional pathophysiological model of post-COVID cardiac involvement was developed and substantiated, comprising:
    - • myocyte injury;
    - • haemodynamic load;
    - • inflammatory-fibrotic remodelling;
    - • electrophysiological vulnerability.
3. The concept that post-COVID cardiac involvement is not a uniform nosological entity but a heterogeneous syndrome with distinct clinical phenotypes was confirmed.
4. The principal clinical phenotypes of post-COVID cardiac involvement were distinguished:
    - • arrhythmic phenotype;
    - • heart-failure/haemodynamic phenotype;
    - • remodelling phenotype;
    - • mixed phenotype.
5. Atrial rhythm disorders were shown to have a leading role in the clinical expression of post-COVID cardiac involvement, supporting the role of atrial remodelling after SARS-CoV-2 infection.

**B. Original scientific findings**

1. Troponin T was shown not necessarily to have strong between-group discriminatory value between patients with and without previous COVID-19, but to have high internal phenotypic value as an independent predictor of reduced left ventricular systolic function.
2. Troponin T was the strongest laboratory marker of LVEF <50% in the analysed cohort, extending its role from an acute injury marker to an indicator of post-COVID myocardial vulnerability.
3. NT-proBNP was elevated in a substantial proportion of patients with preserved or mildly reduced ejection fraction, supporting the presence of a subclinical HFpEF-/HFmrEF-like post-COVID profile.
4. Lower ejection fraction was identified as an independent predictor of an adverse arrhythmic phenotype.
5. For the first time in this cohort, the independent role of Galectin-3 as a marker of post-COVID inflammatory-fibrotic remodelling was demonstrated.
6. Galectin-3 was shown to provide information beyond troponin T and NT-proBNP and to reflect a distinct biological axis: structural remodelling and interstitial fibrosis.
7. Associations were demonstrated between Galectin-3 and echocardiographic indices (volumes, diastolic parameters, LAVI, and LVEF), supporting its role as a biomarker of an adverse structural phenotype.
8. Galectin-3 was proposed as a potential component of future post-COVID risk-stratification algorithms.

**C. Practical and applied contributions**

1. An applicable clinical framework was created for cardiological assessment of patients after COVID-19, based on phenotyping rather than isolated diagnoses.
2. The findings can be implemented in outpatient and inpatient practice in patients with palpitations, dyspnoea, tachycardia, new-onset atrial fibrillation, or suspected post-inflammatory remodelling.

3. The need for follow-up of patients with persistent symptoms after COVID-19 using an integrated cardiological approach is supported.
4. The data provide a basis for future prospective studies of Galectin-3, strain echocardiography, CMR, and multibiomarker panels.

**Overall contribution of the dissertation**

The present dissertation expands existing knowledge of cardiovascular consequences after COVID-19 by demonstrating that post-COVID cardiac involvement is a multicomponent syndrome in which arrhythmias, myocardial injury, haemodynamic stress, and inflammatory-fibrotic remodelling interact. The work introduces Galectin-3 as a significant independent biomarker in post-COVID cardiology and proposes a new clinically applicable concept for phenotyping and risk stratification.

## VIII. PUBLICATIONS AND CONGRESS PARTICIPATION RELATED TO THE DISSERTATION

### 8.1 Publications:

1. **Yovchev Z**, Gospodinov K, Todorova Y, Tisheva-Gospodinova S (2024) ***Association between rhythmconduction disorders and COVID-19 infection.*** Journal of Biomedical and Clinical Research 17(2): 177–186 ;
2. Gospodinov K, Todorova Y, **Yovchev Zh.**, Tisheva-Gospodinova S. Rhythm and conduction disorders in COVID-19. Medinfo. Issue 9, 2022.
3. **Zhivko Yovchev**, Konstantin Gospidinov, G. Todorov, Snejana Tisheva. **Rhythm and Conductive Disorders and COVID-19 Infections.** Jubilee Scientific Conference with International Participation "50 Years of Medical Education and Science in Pleven", 1–3 November 2024. Pleven: Medical University – Pleven; 2024. p. 109. ISBN 978-954-756-347-6.
4. **Yovchev Zh.,** Gospodinov K, Tisheva-Gospodinova S. **Characteristics of the clinical presentation of rhythm and conduction disorders among patients with COVID-19 in the Pleven region.** Medinfo. Issue 4, 2024.

**8.2 Participation in scientific forums:**

1) Lead author of an accepted abstract and poster presentation at the XVII National Congress of Cardiology, Albena, 2022.

2) Lead author of an accepted abstract and poster presentation at the XVIII National Congress of Cardiology, Plovdiv, 2024.

3) Lead author of an accepted abstract and poster presentation at the XX International Medical Conference for Students and Young Doctors, Medical University – Pleven, 2023.

4) Lead author with an oral presentation and abstract at the Jubilee Scientific Conference with International Participation “50 Years of Medical Education and Science in Pleven”, 2024.

5) Lead author with an oral presentation at the National Cardiology Symposium “New Aspects in the Clinical Application of Oral Anticoagulants”, 2023.

6) Case-report presentation at the School for Cardiology Trainees, Hisarya, 2022.

7) Case-report presentation at the XI National Conference Varna ECHO, 2023.

8) Case-report presentation at the Hypertension Conference, Pleven, 2023.

9) Lecturer at the National Symposium “Arteriale Junior”, Sozopol, 2025.

10) Lecturer at the National Symposium “Atrial Fibrillation”, 14–15 November 2025, Novotel Hotel, Sofia.

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