

Cardiopulmonary profiles in severe and critical COVID-19: troponin patterns, transferrin-linked atrial fibrillation, and early pulmonary recovery

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ABSTRACT

Introduction: Cardiovascular and respiratory involvement significantly contributes to COVID-19 severity. This study evaluated cardiorespiratory involvement in severe and critical COVID-19, including troponin-defined myocardial injury patterns, Holter rhythm findings, and early post-discharge outcomes.

Material and Methods: We conducted a prospective observational cohort study of 172 patients hospitalized with severe or critical COVID-19, analyzing clinical, inflammatory, thrombotic, and myocardial injury biomarkers (hs-cTnT, TnI, IL-6, hs-CRP, transferrin, D-dimers) on days 3–5. Troponin-defined injury patterns were analyzed in patients with both hs-cTnT and TnI measurements available. An exploratory Holter substudy (n=24) and a 3-week post-discharge re-evaluation assessed early cardiac and respiratory outcomes.

Results: Among 132 patients with both hs-cTnT and TnI measurements available, the proportion of critical disease increased progressively across troponin elevation patterns (normal, isolated hs-cTnT, combined elevation: 27.9%, 62.5%, 84.6%; $p < 0.001$). After adjustment for age, chronic kidney disease, and cardiovascular disease, isolated hs-cTnT (aOR 4.34; 95% CI 1.67–11.29) and combined elevation (aOR 17.96; 95% CI 3.16–102.04) remained independently associated with critical disease. Newly detected AF occurred in 6/24 patients; transferrin was inversely correlated with AF burden ($\rho = -0.638$; $p = 0.001$; $n = 23$), persisting after adjustment (partial $\rho = -0.649$; $p = 0.002$). Each additional 5 days of oxygen therapy increased odds of fibrotic-like pulmonary changes (aOR 1.60; 95% CI 1.04–2.47; $p = 0.034$). At re-evaluation, biological improvement coexisted with residual pulmonary changes in 14/25 (56%) patients.

Conclusions: Troponin elevation patterns, largely reflecting differing assay sensitivity, were associated with cardiorespiratory severity. Myocardial injury, hypoxemia, pulmonary involvement, and new-onset atrial fibrillation characterized more severe clinical profiles, while the association between transferrin and AF burden warrants further investigation.

Keywords: COVID-19, myocardial injury, troponin T, troponin I, atrial fibrillation, electrocardiography, transferrin.

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INTRODUCTION

SARS-CoV-2 infection can go beyond the scope of acute viral pneumonia, particularly in patients with severe and critical forms of the disease, in whom hypoxemia, systemic inflammation, endothelial dysfunction,

coagulation activation, and hemodynamic stress may coexist and mutually exacerbate one another [1,2].

In the acute phase, cardiovascular manifestations associated with COVID-19 include myocardial injury evidenced by elevated troponin levels, myocardial ischemia, heart failure, arrhythmias, myocarditis, and

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thromboembolic events. Although high-sensitivity cardiac Troponin T (hs-cTnT) and cardiac troponin I (TnI) both reflect myocardial injury, their differing analytical sensitivities were considered when interpreting their parallel assessment in this study, which was used to characterize patterns of myocardial injury rather than to imply distinct pathophysiological entities. However, the interpretation of elevated troponin levels requires clinical and imaging evaluation, as this may reflect heterogeneous mechanisms—ranging from myocardial injury secondary to hypoxemia and inflammation to ischemia, coronary microvascular dysfunction, or direct myocardial damage—without automatically equating to myocarditis [1]. Electrocardiographic and echocardiographic abnormalities have been described in patients with elevated cardiac biomarkers, supporting the existence of a broad spectrum of cardiovascular involvement [3]. Longitudinal studies have highlighted associations between troponin and markers of systemic inflammation, suggesting an interaction between the inflammatory response, COVID-19-associated coagulopathy, tissue hypoxia, and myocardial damage [4,5].

Within this biological profile, transferrin represents a potentially relevant marker, though it has been studied less extensively than IL-6, C-reactive protein, ferritin, or D-dimers. Available data indicate that low transferrin levels are associated with more severe forms of COVID-19 and a more intense inflammatory response, characterized by elevated levels of IL-6, CRP, and ferritin [6,7]. Since transferrin is influenced by inflammation, nutritional status, and iron metabolism, its assessment alongside troponin and other biomarkers may help characterize a more complex biological phenotype in critically ill patients. However, the relationship between transferrin and myocardial injury, as well as between transferrin and arrhythmias, remains insufficiently clarified.

Myocardial injury may be accompanied by electrical instability. During hospitalization, atrial fibrillation, supraventricular tachyarrhythmias, ventricular ectopy, and QTc prolongation have been reported. A meta-analysis involving over 12,000 patients estimated an overall prevalence of arrhythmias of approximately 10%, with a higher frequency in critically ill patients and those with an unfavorable clinical course [8]. New-onset atrial fibrillation has also been associated with more severe inflammation and higher troponin levels in cohorts of hospitalized patients [9]. Holter electrocardiographic monitoring can identify paroxysmal

episodes of atrial fibrillation or ectopy that are not captured by a standard electrocardiogram or intermittent clinical monitoring.

Recovery from an acute infectious episode is an essential component of the clinical burden of the disease. Post-hospitalization follow-up data show that respiratory functional abnormalities may persist, and reduced alveolar-capillary diffusion capacity and restrictive changes are among the findings frequently reported in early evaluations [10,11]. In a prospective multicenter cohort, an assessment conducted approximately 45 days after discharge identified impairments in lung function and exercise capacity, which were more pronounced in patients who required admission to the intensive care unit and mechanical ventilation [12]. These observations support the relevance of an early post-discharge follow-up window - close enough to the infectious episode to capture persistent respiratory dysfunction, yet distinct from the acute phase dominated by instability and interventions to support vital functions. In the present study, an earlier re-evaluation, at three weeks after discharge, was chosen in order to capture the earliest phase of biological and pulmonary recovery.

Although the literature has characterized myocardial injury, arrhythmias, and pulmonary sequelae separately, there are few studies that simultaneously integrate cardiac biomarkers, inflammatory and coagulation markers, oxygenation parameters, prolonged electrical monitoring, and post-discharge pulmonary assessment. Therefore, the objective of this study was to perform a multidimensional characterization of cardiac and respiratory involvement in severe and critical COVID-19, with a focus on the relationship between patterns of myocardial injury, electrical instability, and early pulmonary recovery. The main clinical outcome was the maximum COVID-19 severity reached during hospitalization (critical versus severe), analyzed in relation to hs-cTnT/TnI-defined troponin elevation patterns. In-hospital mortality was evaluated as an additional clinical outcome. Secondary objectives included: evaluating associations between markers of myocardial injury, inflammation, coagulation, and the severity of pulmonary involvement; an exploratory characterization of the arrhythmic profile via Holter monitoring and its relationship with biomarkers; and assessing biological and pulmonary outcomes 3 weeks after discharge.

METHODS

Study Design and Setting

A prospective observational cohort study was conducted, including patients with SARS-CoV-2 infection confirmed by RT-PCR who were hospitalized in the Infectious Diseases Clinic I and/or the Intensive Care Unit of Mureș County Clinical Hospital between November 2020 and March 2022. Prospective enrolment with writ-

ten informed consent began on 21 December 2020, following ethics committee approval. Patients presenting with severe or critical COVID-19, defined per WHO criteria [13], were included. The study is reported per STROBE recommendations [14]; patient flow, including the number available for each analysis, is shown in Figure 1. Part of this cohort has also been analyzed in a separate study addressing a different research question, with no overlap in the analyses reported here.

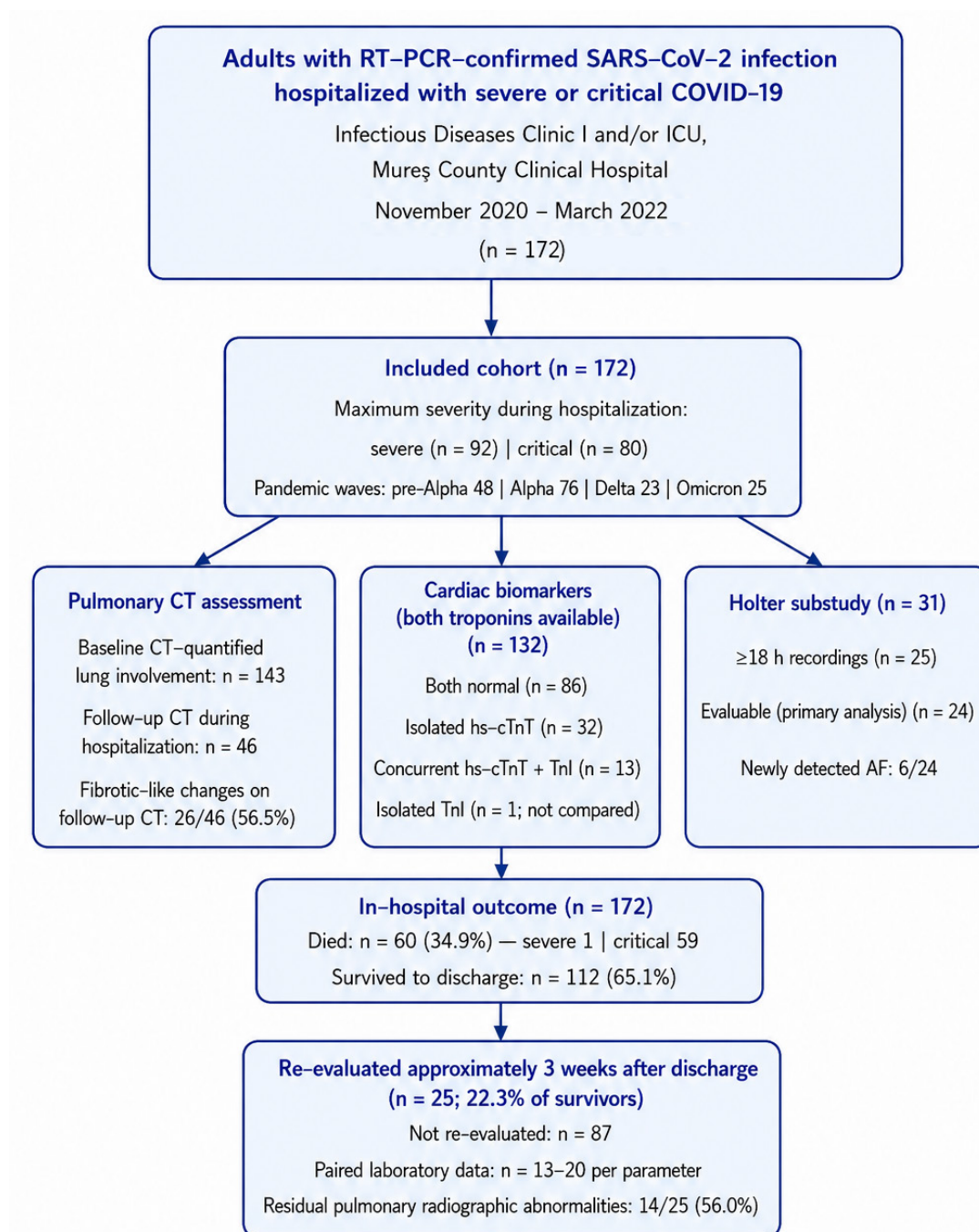


Figure 1. Flow of patients through the study.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committees of the Mureș County Clinical Hospital (approval no. 18923/21.12.2020) and of the George Emil Palade University of Medicine, Pharmacy, Science and Technology of Târgu Mureș (approval no. 1249/28.01.2021); study-specific biomarker assays were introduced after the university approval, accounting for their availability in only a subset of the cohort. Written informed consent was obtained from all patients at the time of enrolment, before any subsequent clinical deterioration; clinical and paraclinical data were handled confidentially and anonymized prior to statistical analysis.

Severe COVID-19 was defined by the presence of pneumonia associated with at least one of the following: peripheral oxygen saturation below 90% in room air, respiratory rate above 30 breaths per minute, or clinical signs of severe respiratory distress, while the critical form was defined by the presence of acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions requiring life-support measures, including invasive or non-invasive mechanical ventilation and/or the administration of vasopressors.

Inclusion and Exclusion Criteria

Inclusion criteria were: age ≥ 18 years; SARS-CoV-2 infection confirmed by RT-PCR; presence of a severe or critical form of COVID-19 at enrollment; and written informed consent. For comparative analyses based on severity, patients were classified according to the maximum severity reached during hospitalization, with those who progressed from severe to critical reclassified into the critical group; this classification was applied consistently throughout. Patients under 18, those with mild or moderate COVID-19, and those transferred to another facility before the outcome was determined were excluded. Patients were not excluded for missing data on individual variables; analyses used available data, with denominators reported for each analysis.

Data Collection and Variables

Demographic, clinical, biological, and imaging data were collected prospectively from medical records during hospitalization. Variables included respiratory parameters, comorbidities, oxygen therapy, ICU admission, and length of stay. For the Holter subgroup, concomitant treatments relevant to biomarkers/

rhythm (corticosteroids, tocilizumab, remdesivir, anticoagulation) and QT-prolonging antibiotic exposure were recorded; none received azithromycin, one received levofloxacin.

Pandemic waves were assigned by predominant circulating SARS-CoV-2 variant at admission: pre-Alpha (through Feb 28, 2021), Alpha (Mar 1–Jun 30, 2021), Delta (Jul 1–Dec 31, 2021), and Omicron (from Jan 1, 2022), based on reported variant prevalence in Romania and Europe [15], since individual sequencing was unavailable.

Respiratory impairment was characterized by SpO₂ at admission and its lowest value during hospitalization, oxygen therapy need/duration, and CT-assessed lung involvement extent. The lowest SpO₂ value was used as the hypoxemia indicator in subsequent analyses.

Holter monitoring was performed as part of the same protocol, depending on device availability. A subgroup was re-evaluated ~3 weeks after discharge to assess early biological and respiratory outcomes; this was planned for all patients discharged alive. Of 112 survivors, 25 (22.3%) attended follow-up and constituted this subgroup; reasons for non-attendance were not systematically documented.

Laboratory Tests

Biological assessment included markers of inflammation, hematological and coagulation parameters, and myocardial injury markers. Per protocol, IL-6, D-dimers, hs-cTnT, TnI, hs-CRP, and transferrin were scheduled for measurement on days 3–5 of hospitalization, defining a prespecified time window for these assessments. Biomarker availability varied across patients because blood sampling could not always be completed within this window, some collected samples were unsuitable for analysis, or patients had been transferred to the intensive care unit before protocol-specified sampling could be performed.

High-sensitivity C-reactive protein (hs-CRP) and transferrin were measured by immunonephelometry (BN ProSpec, Siemens Healthineers); hs-CRP reference ≤ 3 mg/L, lower analytical limit 0.161 mg/L; transferrin reference 2.0–3.6 g/L. Both admission and peak ferritin values were analyzed.

TnI and hs-cTnT were measured on the same platform (cobas e 411; Roche Diagnostics, Mannheim, Germany) by electrochemiluminescence immunoassay. TnI (conventional-sensitivity assay; limit of detec-

tion 0.16 ng/mL) was expressed in ng/mL and hs-cTnT in ng/L. Elevation was defined by assay-specific 99th-percentile upper reference limits (>0.16 ng/mL for TnI, >14 ng/L for hs-cTnT), per the Fourth Universal Definition of Myocardial Infarction [16]; this analytical sensitivity difference was considered when interpreting troponin patterns. Patients with available measurements for both troponins were classified into four categories: both troponins within the reference range, isolated elevation of hs-cTnT, isolated elevation of TnI, and concurrent elevation of hs-cTnT and TnI. Because the isolated-TnI category included only one patient, it was excluded from the statistical comparison among groups.

Tissue injury was characterized using peak LDH and CK during hospitalization; IL-6 and LDH were analyzed as continuous variables without cut-off-based classification.

Pulmonary Imaging Assessment

Initial pulmonary imaging was performed by chest CT at hospital admission; involvement extent was visually estimated by the reporting radiologist as a percentage of affected parenchyma (no automated software used). CT was repeated when clinically warranted, with reports from multiple radiologists as part of routine care. Fibrotic-like changes were recorded when described in CT reports; no centralized re-reading was performed.

Holter electrocardiographic monitoring and rhythm analysis

Within the main cohort, an exploratory Holter ECG substudy was conducted depending on monitor availability, without selection based on prior arrhythmia history. Monitoring was scheduled for 24 h and was initiated when the device became available. Monitoring was performed in 31 patients using a BTL-08 Holter H600 recorder (BTL Industries Ltd., UK), with the manufacturer's analysis software and physician review. Recordings ≥ 18 hours with interpretable key parameters were included in the main analysis; shorter recordings were evaluated descriptively. Parameters included heart rate, AF presence/burden (% of analyzable recording time), ventricular/supraventricular ectopy, complex ectopy (couplets/triplets/bigeminy/trigeminy), and Bazett-corrected QTc; AF episodes were confirmed by a cardiologist. Holter timing (days from admission) and COVID-19 severity at monitoring were also recorded.

Clinical Follow-up

Three weeks after discharge, pulmonary imaging was performed primarily by chest X-ray (one patient additionally underwent CT for suspected pleuropulmonary complication), classified by presence/absence of residual changes. Spirometry was available in only 6 patients (analyzed descriptively); DLCO was not assessed. For longitudinal analysis, CRP, NLR, platelet count, LDH, AST, ALT, ferritin, and creatinine at re-evaluation were compared with admission values using paired data.

Statistical Analysis

Continuous variables were summarized as mean $\pm$ standard deviation or median [interquartile range, IQR], as appropriate.

Comparisons between two independent groups were performed using the Mann-Whitney U test for continuous variables, and the Kruskal-Wallis test was used for comparisons among more than two independent groups. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Given the distributional characteristics of several continuous variables and the inclusion of ordinal variables in some analyses, associations were assessed using Spearman's rank correlation coefficient (ρ).

For analyses involving multiple comparisons, p-values were adjusted using the Benjamini-Hochberg procedure (FDR), with q-values reported for each family: the 36 Figure 2 correlations; the 5 peak-ferritin correlations; the 28 Holter biomarker-rhythm associations; and the longitudinal comparisons. Tables 1 and 2 report unadjusted p-values. Holter analyses ($n=24$) were exploratory; AF timing was compared using the Mann-Whitney U test, and its association with AF burden and with transferrin (partial correlation adjusted for age, severity, and monitoring interval; bootstrap 95% CI, 50,000 replicates) used Spearman's correlation.

Multivariable logistic regression assessed troponin pattern associations with critical disease/mortality (reference: both troponins normal), adjusted for age, chronic kidney disease, and cardiovascular disease, reported as aORs with 95% CIs. Similarly, oxygen therapy duration and fibrotic-like changes were assessed by logistic regression adjusted for age and baseline CT involvement (per 10-year, 10-percentage-point, and 5-day increases respectively; $n=46$, 26 events); this exploratory analysis was also tested in a survivors-only sensitivity analysis.

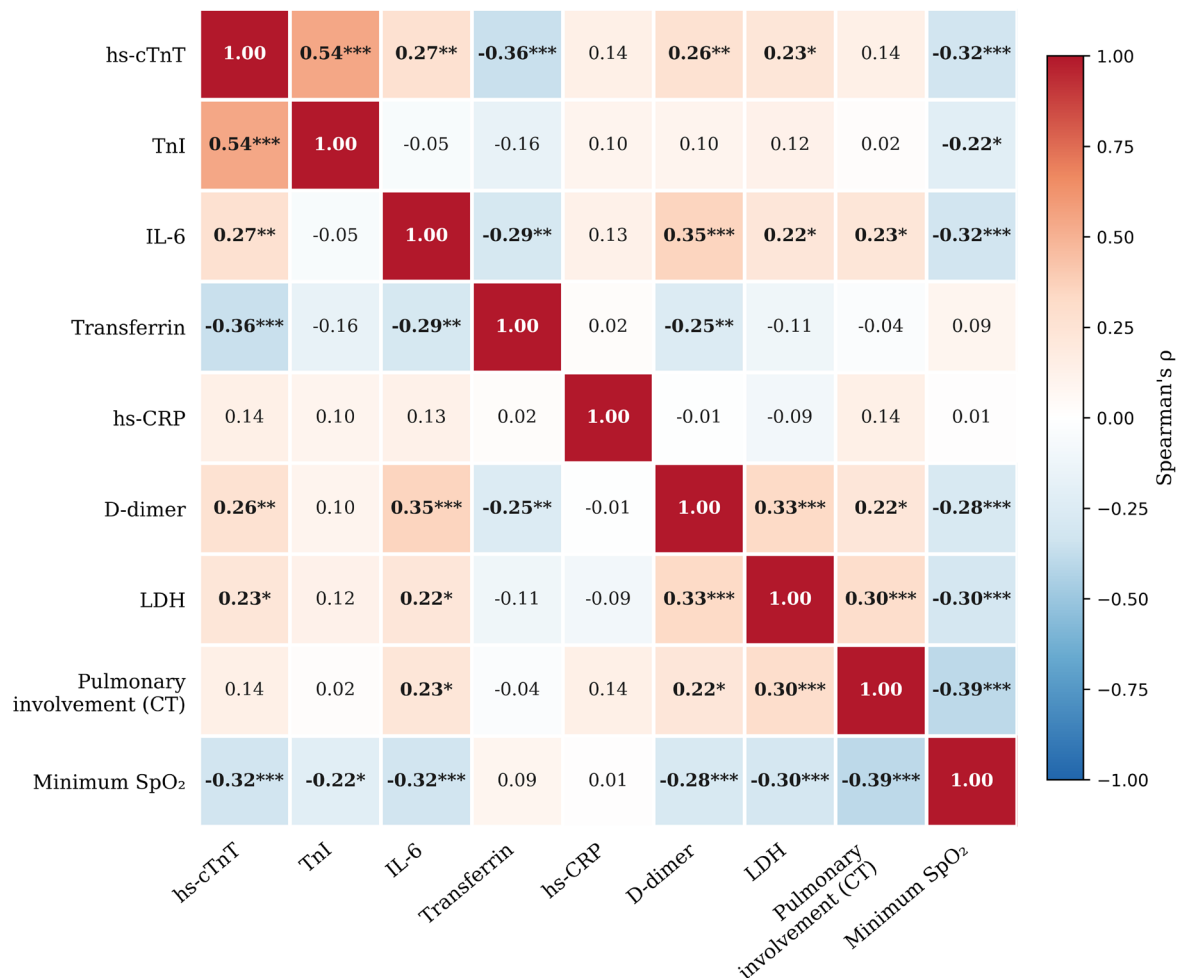


Figure 2. Spearman correlations between biomarkers and cardiorespiratory variables. Note: Color intensity reflects the strength and direction of the correlation coefficient (ρ). * $p < 0.05$, ** $p < 0.01$, * $p < 0.001$.**

Longitudinal biological values (admission vs. re-evaluation) were compared using the Wilcoxon signed-rank test on complete pairs, with Benjamini–Hochberg FDR correction. All tests were two-sided; $p < 0.05$ and $q < 0.05$ (FDR-adjusted) were considered significant.

Statistical analyses were performed using IBM SPSS Statistics, version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

General Characteristics of the Study Population

Of the 172 patients, 92 (53.5%) were classified with severe disease and 80 (46.5%) with critical disease; the severity classification corresponded to actual ICU trans-

fer in 160/172 cases (93.0%). The median age was 67 [IQR 54–77] years, and 106 patients (61.6%) were men (Table 1). The median time from symptom onset to hospital admission was 6 days [IQR 4–8]. The distribution of critical cases differed between waves ($p = 0.002$), with the highest proportions observed in the Delta and Omicron waves. The median length of hospitalization in the analyzed cohort was 14 [IQR 11.0–18] days, and the median length of stay in the intensive care unit was 9 [6–16] days. At admission, peripheral oxygen saturation had a median value of 89 [85–91]%, and in patients with quantifiable imaging findings ($n = 143$), the median extent of pulmonary involvement on CT was 45 [30–60]% (Table 1).

Overall, 60 of 172 patients (34.9%) died during hos-

Table 1. Clinical and biological characteristics according to maximum COVID-19 severity during hospitalization

Variable	Severe (n=92)	Critical (n=80)	p-value
Age, years	63.5 [53.0–74.0]	72.0 [61.8–79.0]	<0.001
Male, n (%)	63 (68.5)	43 (53.8)	0.048
Hypertension, n/N (%)	52/92 (56.5)	49/80 (61.3)	0.530
Pre-existing cardiovascular disease, n/N (%)	22/92 (23.9)	32/80 (40.0)	0.017
Diabetes mellitus, n/N (%)	18/92 (19.6)	17/80 (21.25)	0.720
Chronic kidney disease, n/N (%)	6/92 (6.5)	12/80 (15.0)	0.061
Pandemic wave, n (%)			0.002
Pre-Alpha	30 (32.6)	18 (22.5)	
Alpha	47 (51.1)	29 (36.3)	
Delta	5 (5.4)	18 (22.5)	
Omicron	10 (10.9)	15 (18.8)	
Vaccinated, n (%)	0/92 (0.0)	5/80 (6.3)	0.020
Length of hospital stay, days	13.5 [11.8–16.0]	15.0 [9.5–22.0]	0.436
Admission SpO ₂ , %	89.5 [86.8–92.0]	88.0 [83.0–90.0]	0.009
CT lung involvement, % (n=143)	35.0 [25.0–45.0]	50.0 [35.0–65.0]	<0.001
Duration of oxygen therapy, days	9.0 [5.2–12.0]	13.5 [9.0–20.0]	<0.001
D-dimer, µg/mL	0.65 [0.41–1.49]	1.38 [0.46–3.73]	0.015
IL-6, pg/mL	51.5 [16.5–94.3]	89.9 [53.7–250.9]	<0.001
hs-CRP, mg/L	18.1 [4.1–43.2]	14.2 [2.8–79.8]	0.760
Transferrin, g/L	1.74 [1.43–2.09]	1.51 [1.09–1.88]	0.083
Maximum CK, U/L	111.0 [55.8–266.0]	224.5 [98.0–574.8]	0.003
TnI >0.16 ng/mL, n/N (%)	2/76 (2.6)	12/56 (21.4)	<0.001
hs-cTnT >14 ng/L, n/N (%)	14/78 (17.9)	32/60 (53.3)	<0.001
Corticosteroids, n/N (%)	91/92 (98.9)	78/80 (97.5)	0.598
Tocilizumab, n/N (%)	10/92 (10.9)	14/80 (17.5)	0.271
Anticoagulation, n/N (%)	90/92 (97.8)	78/80 (97.5)	1.000
In-hospital mortality, n (%)	1 (1.1)	59 (73.8)	<0.001

Note: Data are presented as median [interquartile range, IQR] for continuous variables and n (%) for categorical variables. Denominators vary according to data availability. Between-group comparisons were performed using the Mann–Whitney U test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables, as appropriate. The p-value for the pandemic wave represents the overall comparison across the four categories. Reported p-values are unadjusted. Data are median (IQR) or n (%). GCS = Glasgow Coma Scale; WFNS = World Federation of Neurosurgical Societies. Mann–Whitney U test was used for continuous variables, chi-square with continuity correction or Fisher exact test for categorical variables. Modified Fisher score was available in 104/127 patients.

pitalization, while 112 (65.1%) survived to discharge.

Integrated Relationship Between Myocardial Injury, Inflammation, and Pulmonary Involvement

Spearman's correlation analysis revealed significant interrelationships between inflammatory/prothrombotic markers, myocardial injury, and pulmonary involvement severity (Figure 2). The strongest associations were between hs-cTnT and TnI ($\rho=0.544$; $p<0.001$; $q<0.001$), between CT-detected pulmonary involvement and minimum SpO₂ ($\rho=-0.393$; $p<0.001$; $q<0.001$), and between IL-6 and D-dimers ($\rho=0.353$; $p<0.001$; $q=0.001$). hs-cTnT was also inversely correlated with transferrin and minimum SpO₂ and positively with LDH; IL-6 and D-dimers were each also correlated with CT involvement (Figure 2). All associations remained significant after Benjamini–Hochberg correction for multiple testing.

In a further exploratory analysis, the peak ferritin level during the acute episode correlated positively

with LDH ($\rho=0.407$; $p<0.001$; $q<0.001$), the extent of pulmonary involvement on CT ($\rho=0.207$; $p=0.014$; $q=0.015$), hs-cTnT ($\rho=0.228$; $p=0.012$; $q=0.015$), and TnI ($\rho=0.226$; $p=0.015$; $q=0.015$), and negatively correlated with minimum SpO₂ ($\rho=-0.335$; $p<0.001$; $q<0.001$). The maximum ferritin level was recorded at a median of 10 [5.25–15] days after symptom onset.

Myocardial injury patterns defined by troponin patterns

Of the 132 patients with available measurements for both troponins, 86 (65.2%) had normal levels of both biomarkers, 32 (24.2%) had an isolated elevation of hs-cTnT, and 13 (9.8%) had a concurrent elevation of both hs-cTnT and TnI (Table 2); one patient with an isolated elevation of TnI was excluded from the three-group comparison. The distribution of troponin patterns did not differ significantly across pandemic waves ($p=0.395$). The prevalence of critical disease, the severity of hypoxemia, and the duration of oxygen therapy

Table 2. Clinical and biological characteristics according to troponin-defined myocardial injury patterns

Parameter	Both troponins within the reference range (n=86)	Isolated hs-cTnT elevation (n=32)	Combined hs-cTnT and TnI elevation (n=13)	p-value
Age, years	61 [51.0–68.0]	77 [62.8–83.3]	72 [68.0–79.0]	< 0.001
Critical COVID-19, n (%)	24 (27.9)	20 (62.5)	11 (84.6)	< 0.001
Minimum SpO ₂ , %	87 [81.3–89.0]	82 [75–85.5]	79 [75–84]	0.002
CT lung involvement, %	40 [25–50]	50 [35–65]	43 [30–62.5]	0.224
Duration of oxygen therapy, days	10 [7–15]	13.5 [9.8–21.3]	15 [8–20]	0.020
Peak LDH, U/L	347.5 [274.3–480.8]	458 [335.8–791.5]	550 [468.0–929.5]	0.004
Peak CK, U/L	101.5 [55–212.8]	174 [95–319]	502 [171.5–1085.8]	0.002
Transferrin, g/L	1.78 [1.46–2.10]	1.35 [0.96–1.67]	1.37 [1.19–1.72]	<0.001
IL-6, pg/mL	50.18 [17.67–118.32]	80.81 [62.92–129.95]	74.16 [56.79–138.68]	0.126
D-dimer, µg/mL	0.58 [0.40–1.29] (n=79)	1.60 [0.45–3.00] (n=31)	0.86 [0.47–3.29] (n=11)	0.136
Chronic kidney disease, n/N (%)	3/84 (3.6)	6/32 (18.8)	2/13 (15.4)	0.013
In-hospital mortality, n/N (%)	11/86 (12.8)	16/32 (50.0)	10/13 (76.9)	<0.001

Notes: Data are presented as median [IQR] or n (%). For continuous variables, the Kruskal-Wallis test was used, and for categorical variables, the χ^2 /Fisher test, as appropriate. hs-cTnT, high-sensitivity cardiac troponin T; TnI, troponin I; SpO₂, peripheral arterial oxygen saturation; LDH, lactate dehydrogenase; CK, creatine kinase. Critical COVID-19 refers to the maximum severity reached during hospitalization.

all showed a progressive gradient across the three groups (Table 2). Peak LDH and CK were highest, and transferrin lowest, in patients with elevated hs-cTnT, particularly in the concurrent hs-cTnT/TnI elevation group; pulmonary CT involvement, IL-6, and D-dimer levels did not differ significantly among the three groups (Table 2).

In multivariable logistic regression adjusted for age, chronic kidney disease, and pre-existing cardiovascular disease, both isolated hs-cTnT elevation and concurrent hs-cTnT/TnI elevation remained significantly associated with critical disease and in-hospital mortality, with the strongest associations observed for concurrent hs-cTnT and TnI elevation (Table 3).

Table 3. Multivariable associations of troponin elevation patterns with critical COVID-19 and in-hospital mortality

Troponin elevation pattern	Critical disease, aOR (95% CI)	p-value	In-hospital mortality, aOR (95% CI)	p-value
Both troponins within the reference range	Reference	—	Reference	—
Isolated hs-cTnT elevation	4.34 (1.67–11.29)	0.003	7.88 (2.66–23.33)	< 0.001
Combined hs-cTnT and TnI elevation	17.96 (3.16–102.04)	< 0.001	40.51 (7.12–230.50)	< 0.001

Note: Multivariable logistic regression models were adjusted for age, chronic kidney disease, and pre-existing cardiovascular disease. Patients with both troponins within the reference range were used as the reference category. Analyses were based on complete cases (n=129). aOR, adjusted odds ratio; CI, confidence interval; hs-cTnT, high-sensitivity cardiac troponin T; TnI, troponin I.

Pulmonary involvement and respiratory support

Imaging-quantified pulmonary involvement was available for 143 patients and was significantly associated with the severity of respiratory failure and the need for respiratory support. In addition to its inverse correlation with minimum SpO₂ (Figure 2), the extent of CT-detected pulmonary lesions was positively correlated with the duration of intensive care unit stay ($\rho = 0.431$; $p < 0.001$) and, to a lesser extent, with the duration of oxygen therapy ($\rho = 0.213$; $p = 0.011$).

Among the 46 patients who underwent repeat CT during hospitalization, fibrotic-like changes were documented in 26 (56.5%). In exploratory multivariable logistic regression adjusted for age and baseline CT involvement, longer oxygen therapy was associated with

fibrotic-like changes (aOR per 5-day increase, 1.60; 95% CI 1.04–2.47; $p=0.034$). The association persisted in the sensitivity analysis restricted to hospital survivors (n=33; 22 events; aOR 2.26; 95% CI 1.12–4.54; $p=0.023$).

Complications during hospitalization included pulmonary thromboembolism (PTE), confirmed in 9/172 patients (5.2%); fibrotic-like pulmonary changes were identified in 26 patients, of whom 14 required home oxygen therapy after discharge.

Exploratory Holter Substudy

Holter monitoring was performed in 31 patients, conducted at a median of 10 [7.0–13.0] days after admission, with a median recording duration of 24 h 10 min

[23 h 44 min–24 h 52 min] all 31 patients. None of the patients monitored had a known history of atrial fibrillation. Of the 25 recordings with a duration of ≥ 18 hours, 24 had complete data for the prespecified rhythm parameters and were included in the primary analysis. All patients included in the main Holter analysis received dexamethasone (24/24), while 20/24 (83.3%) received remdesivir, 6/24 (25.0%) tocilizumab, and 23/24 (95.8%) anticoagulation. Among the 24 patients included in the main Holter analysis, none received azithromycin and one received levofloxacin.

Newly detected atrial fibrillation, confirmed by a cardiologist, occurred in 6 of 24 patients (Table 4). In patients with AF, Holter monitoring tended to be performed later than in those without AF (13.5 [10.0–17.75] vs. 8.5 [5.0–11.0] days; $p=0.070$), without reaching statistical significance. In the exploratory analysis, the interval between admission and Holter monitoring correlated positively with AF burden ($\rho=0.411$; $p=0.046$).

Ventricular and supraventricular ectopy were common (Table 4). The median maximum QTc (Bazett formula) was 469 [457–492] ms; QTc was ≥ 480 ms in 9 patients (37.5%) and ≥ 500 ms in 4 patients (16.7%) (Table 4).

The most distinct biological signal from the Holter substudy was the association between low transferrin levels and newly diagnosed atrial fibrillation. Transferrin was significantly lower in patients with newly diagnosed atrial fibrillation than in those without atrial fibrillation: 1.34 [1.23–1.49] versus 2.17 [1.82–2.65] g/L ($p=0.002$). Furthermore, transferrin concentration was inversely correlated with atrial fibrillation burden ($\rho = -0.638$; $p = 0.001$, $n = 23$).

Among the 28 exploratory biomarker–rhythm correlations, only the inverse association between transferrin and AF burden remained significant after FDR correction ($\rho = -0.638$; $p = 0.001$; $q = 0.030$; $n = 23$; Supplementary Table S1). An adjusted sensitivity analysis is presented in Supplementary Table S2.

Early pulmonary and biological findings

Twenty-five survivors were re-evaluated three weeks after discharge, representing 22.3% of the 112 survivors. Compared with the other 87 patients discharged alive who did not undergo the 3-week reassessment, the 25 re-evaluated patients had a longer duration of oxygen therapy during the acute hospitalization (12 [9–21] vs. 9 [5–13] days; $p=0.007$) and higher peak conventional CRP levels (134.5 [79.4–198.0] vs. 73.4 [32.1–136.1]

Table 4. Holter monitoring characteristics and arrhythmic findings

Parameter	Result
Patients included in the main Holter analysis	24
Time from hospital admission to Holter monitoring, days	9.5 [5.0–11.0]
Recording duration, h:min, median [IQR]	24 h 22 min [24 h 11 min–25 h 06 min], $n=24$
Mean heart rate, bpm	72.5 [64.0–77.0]
Minimum heart rate, bpm	48.0 [44.8–54.5]
Maximum heart rate, bpm	124.0 [102.8–133.0]
Newly detected AF	6/24 (25.0%)
AF burden among AF-positive patients, %	1.5 [1.0–2.0]
Longest AF episode, min	2.9 [1.2–5.1]
PVCs present	20/24 (83.3%)
PVC count/ 24 h	53.4 [23.8–191.0]
Ventricular couplets	9/24 (37.5%)
Ventricular triplets	5/24 (20.8%)
Ventricular bigeminy	14/24 (58.3%)
Complex ventricular ectopy (any)	18/24 (75.0%)
PACs present	22/24 (91.7%)
PAC count/24 h	29.0 [13.3–97.3]
Supraventricular couplets	13/24 (54.2%)
Supraventricular triplets	16/24 (66.7%)
Complex supraventricular ectopy (any)	17/24 (70.8%)
Maximum Bazett-corrected QT interval (QTc), ms	469.0 [457.0–492.2]
Maximum Bazett-corrected QTc ≥ 480 ms	9/24 (37.5%)
Maximum Bazett-corrected QTc ≥ 500 ms	4/24 (16.7%)

Notes: Data are presented as a median [IQR] or n (%), as appropriate. PVC and PAC counts were normalized to 24 hours. AF burden and longest AF episode duration are reported among patients with newly detected AF. AF: atrial fibrillation; PVCs: premature ventricular contractions; PACs: premature atrial contractions.

mg/L; $p=0.009$), whereas age, initial CT lung involvement, hs-CRP, IL-6, transferrin, peak CK, TnI, and hs-cTnT did not differ significantly between groups.

Longitudinal analysis of patients with paired measurements revealed significant improvement across all measured inflammatory and tissue-injury markers, including an increase in platelet count, after FDR correction (Table 5). In contrast to this biological improvement, residual pulmonary radiological abnormalities persisted in 14/25 (56.0%; 95% CI 37.1–73.3%). In an exploratory analysis of acute-phase factors associated

with imaging persistence, the extent of pulmonary involvement on CT tended to be higher in patients with persistently abnormal imaging than in those with normalized imaging (40.0 [35.0–48.8]% vs. 25.0 [22.5–45.0]%; $p=0.096$), without reaching statistical significance. IL-6, D-dimers, transferrin, hs-CRP, hs-cTnT, and TnI measured during the acute phase did not significantly differentiate the two groups. Spirometry was available in six patients at post-discharge follow-up, showing mild ventilatory impairment in four patients and normal findings in two.

Table 5. Biological changes between admission and the 3-week post-discharge re-evaluation

Parameter	Paired n	Admission	3-week follow-up	p-value	FDR q-value*
CRP, mg/L	20	129.55 [76.51–202.41]	8.10 [1.30–14.93]	<0.001	<0.001
NLR	20	7.58 [4.92–8.77]	1.44 [1.12–2.47]	<0.001	<0.001
Platelet count, $\times 10^9$ /L	17	231.85 [187.52–245.57]	272.00 [195.50–330.75]	0.019	0.022
LDH, U/L	17	369 [214–445]	247 [217–275]	0.002	0.003
AST, U/L	15	44 [32.5–65.5]	25 [18.5–52]	0.002	0.003
ALT, U/L	13	69 [40–99]	34 [18–52]	0.005	0.008
Ferritin, [ng/mL]	20	944.65 [653.45–1857.25]	361.40 [208.55–493.23]	<0.001	<0.001
Creatinine, mg/dL	20	0.84 [0.78–0.92]	0.74 [0.70–0.86]	0.070	0.070

Note: *Wilcoxon signed-rank test for paired samples; q-values were obtained using the Benjamini–Hochberg correction across the eight longitudinal comparisons

■ **DISCUSSION**

In this cohort of 172 patients with severe or critical COVID-19, three findings stand out. First, troponin patterns defined a graded severity spectrum, with critical disease rising from 27.9% to 62.5% and 86.4% across normal, isolated hs-cTnT, and concurrent hs-cTnT/TnI elevation groups; both elevated patterns remained independently associated with critical disease and mortality after adjustment for age and cardiorenal comorbidity. Second, prolonged rhythm monitoring uncovered newly detected atrial fibrillation in 6 of 24 patients and complex ventricular ectopy in 75%—an electrical burden a standard ECG would largely have missed. Third, at three weeks after discharge, marked biological improvement coexisted with residual pulmonary abnormalities in 14 of 25 patients. The novelty of this study lies in integrating cardiac, electrical, and pulmonary findings within the same cohort, highlighting their non-parallel evolution beyond the acute phase.

Troponin patterns showed clinically meaningful stratification between isolated hs-cTnT and combined hs-cTnT/TnI elevation. hs-cTnT was measured with a

high-sensitivity assay and TnI with a conventional-sensitivity assay; isolated hs-cTnT elevation may partly reflect detection of lower concentrations undetectable by the TnI assay, explaining the rarity of isolated TnI elevation and arguing against these patterns as biologically distinct phenotypes rather than a severity continuum. Accordingly, these findings should not be interpreted as supporting routine simultaneous measurement of hs-cTnT and TnI, but rather as illustrating how assay characteristics may influence the classification and interpretation of myocardial injury patterns. Consistent with this, troponin patterns tracked respiratory compromise, hypoxemia, and tissue damage—including an inverse association of hs-cTnT with minimum SpO2 and a weaker positive association with LDH and peak CK—supporting elevated troponin as a marker of cardiovascular involvement within a complex systemic disease rather than isolated myocardial infarction or myocarditis [4,17,18].

Cardiac troponin has also been linked to markers of inflammation and coagulation (IL-6, CRP, D-dimers), supporting a cardio-inflammatory and thrombo-inflammatory phenotype [4]; however, the observational design and the measurement of biomarkers within a

common biological window do not allow a complete separation of the contributions of hypoxemia, inflammation, hemodynamic stress or demand ischemia, renal impairment, direct or indirect cardiac involvement, or general tissue damage. Acute kidney injury may additionally influence circulating troponin concentrations in critically ill patients; however, AKI was not systematically defined in our cohort, precluding assessment of its independent contribution to troponin elevation. Both troponin elevation patterns remained independently associated with critical disease and mortality after adjusting for age, chronic kidney disease, and cardiovascular disease, indicating these associations were not explained solely by these comorbidities; however, the very wide confidence interval for the combined elevation pattern (aOR 40.51; 95% CI 7.12–230.5 for mortality) reflects its small size and warrants cautious interpretation.

Peak ferritin showed weak-to-moderate correlations with pulmonary involvement and myocardial injury markers, strongest with LDH and minimum SpO₂. Given heterogeneous measurement timing, these exploratory findings are hypothesis-generating and should not be interpreted as evidence of a direct mechanistic or causal relationship.

Severe pulmonary involvement is a major component of COVID-19, and persistence of structural abnormalities after the acute phase has been documented, particularly in severe pneumonia, aligning with post-COVID studies identifying disease severity, ventilation need, initial CT findings, and hospitalization length as factors associated with long-term pulmonary changes [19–21]. Hălmăciu et al. reported correlations between CT-quantified lung involvement and IL-6, with higher imaging burden linked to unfavorable prognosis [22]. In our cohort, longer oxygen therapy was associated with fibrotic-like changes even after adjusting for age and baseline CT involvement, though oxygen duration more likely reflects an integrated marker of respiratory impairment than a direct causal factor. Repeated CT was clinically indicated rather than protocol-driven, so patients with more severe courses may have been more likely to undergo repeat imaging; the association nonetheless persisted in a survivors-only sensitivity analysis. Given the limited sample size and non-standardized indication, these findings remain exploratory and hypothesis-generating.

Arrhythmias are frequently reported in COVID-19, particularly in severe cases, attributed to systemic in-

flammation, hypoxemia, metabolic/electrolyte imbalance, and cardiovascular stress [8,9]. The Holter substudy revealed a high prevalence of electrical abnormalities—ectopy, prolonged QTc, and newly detected AF—suggesting the electrical profile of severe/critical COVID-19 may be more complex than captured by standard ECG. However, these exploratory substudy does not establish the clinical or prognostic utility of routine Holter monitoring. These prevalences must be interpreted given the small substudy size and selected monitored population, and cannot be extrapolated to the full cohort; QTc prolongation in particular should be interpreted cautiously, as contemporaneous electrolyte levels and QT-prolonging medication exposure were not systematically available.

An exploratory finding of interest was the inverse association between transferrin—a negative acute-phase reactant linked to more intense inflammation in COVID-19 [6]—and AF burden, which remained significant after correction for multiple testing; since AF burden was zero in patients without AF, this largely reflects the transferrin difference between patients with and without AF. This finding is consistent with evidence independent of COVID-19: a Mendelian randomization study found genetically determined transferrin inversely associated with AF risk, while higher iron, ferritin, and transferrin saturation were associated with higher AF risk [23], and altered iron metabolism has been implicated in the arrhythmic substrate through oxidative stress, disrupted calcium homeostasis, and atrial electrical/structural remodeling [24]. In this context, the association observed in our cohort may reflect interaction between systemic inflammation, disrupted iron homeostasis, and atrial electrical vulnerability, without demonstrating a direct arrhythmogenic effect of transferrin. However, given the small substudy size, low AF count, and selected nature of the monitored subgroup, transferrin cannot be considered a validated arrhythmic-risk biomarker; this association should be regarded as hypothesis-generating, requiring confirmation in independent cohorts with standardized rhythm monitoring.

The coexistence of marked biological improvement with persistent pulmonary imaging changes suggests a temporal dissociation between systemic resolution and pulmonary structural recovery, consistent with post-severe-COVID-19 pulmonary abnormalities described elsewhere [25–27], though this should be interpreted cautiously given the small re-evaluated sample and

predominant use of chest X-rays.

■ STUDY LIMITATIONS

Main limitations include the single-center design; the small Holter subgroup and non-standardized timing of Holter monitoring due to device availability; the small re-evaluation subgroup; clinically indicated, non-protocol-driven imaging re-evaluations; and available-case handling of missing data. Holter and biomarker associations are exploratory, and the observational design precludes causal inference. Differing analytical sensitivities of hs-cTnT and TnI may have shaped the observed troponin patterns, and Holter findings may reflect selection bias and residual confounding, including incomplete QT-prolonging factor data. Repeat CT was not centrally re-read, and fibrotic-like changes should not be equated with established fibrosis. Post-discharge follow-up was limited to 25/112 discharged patients over roughly three weeks, predominantly by chest radiography, with spirometry in only six patients and no systematic DLCO assessment. Inclusion across multiple pandemic waves is a further heterogeneity source—patient profile and critical-case proportion varied by period, consistent with other multi-wave cohorts [28], which together with admission of already advanced disease may partly explain the high in-hospital mortality and limits generalizability to later phases. Vaccination coverage was very low (2.9%) and confined to the critical group, precluding assessment of vaccine effectiveness.

■ CONCLUSIONS

Troponin patterns, arrhythmic burden, and pulmonary recovery evolved independently in this cohort, indicating that cardiopulmonary impairment after severe or critical COVID-19 is multidimensional and does not resolve in parallel. These findings highlight the potential value of underscore the multidimensional nature of cardiopulmonary involvement beyond the acute phase, while the association between transferrin and AF burden warrants further investigation in larger cohorts with standardized rhythm monitoring.

■ SUPPLEMENTARY MATERIALS:

The following supporting information can be downloaded at: Table S1: Exploratory correlations between

biomarkers and rhythm parameters in the Holter sub-study; Table S2: Sensitivity analyses of the association between transferrin and atrial fibrillation burden.

■ AUTHOR CONTRIBUTIONS:

Conceptualization, V.N. and A.M.V.; methodology, V.N., A.M.V., and A.V.; investigation, V.N. and A.V., I.T.; data curation, V.N. and T.F.; formal analysis, V.N. and T.F.; validation, V.N., A.V., I.T., T.F., and A.M.V.; visualization, V.N. and T.F.; writing—original draft preparation, V.N. and A.M.V.; writing—review and editing, V.N., A.M.V. and A.V., V.N.; supervision, A.M.V.; project administration, V.N. and A.M.V. All authors read and approved the final version of the manuscript.

Data Availability Statement:

The data presented in this study are available from the corresponding author upon reasonable request.

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Conflicts of Interest

None declared.

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