Criteria and definitions

Unspecific abnormal findings: history not related to risk factors for COVID-19, current symptoms not related to the cardiovascular system, electrocardiogram (EKG) with signs of left ventricular hypertrophy or left QRS-axis deviation, echocardiogram evidencing mild left ventricle hypertrophy, mild diastolic dysfunction, mild cardiac chamber enlargement and isolated left anterior hemiblock (LAHB). All the alterations in the basic routine lab tests were considered unspecific.

Suspicious abnormal findings: current potentially cardiovascular symptoms (dyspnea, precordialgia, palpitations), basal sinus tachycardia or bradycardia, signs compatible with heart valve diseases or heart failure, heart arrhythmias, conduction disorders, drop in ejection fraction (EF) or EF < 40 % and wall motion abnormalities.

Ventricular dysfunction criteria: progression of functional class with no other non-cardiovascular explanation and/or signs of heart failure and/or drop in EF and/or increased pro-BNP.

Risk factors for COVID-19 severity: prior heart disease, overweight, diabetes, chronic obstructive pulmonary disease (COPD)/asthma and immunodepression.

Severity of the acute stage of COVID-19

- Mild: patients who did not require hospitalization or O_2 supply.
- Moderate: patients who required hospitalization and O_2 supply in the general hospitalization room.
- Severe: patients who required high-flow oxygen therapy (HFOT) or admission to the intensive care unit (ICU) with or without mechanical ventilation (MV).
- Sinus tachycardia (ST): resting heart rate (HR) ≥ 100 bpm and sinus bradycardia (SB): resting HR ≤ 50 bpm assessed by physical examination.

Statistics

A predictive model was built to assess the group of covariables that best forecast the risk of de novo heart disease among post-COVID-19 patients. The variables were analyzed as to their prevalence and distribution.

The relationship of each variable with mortality was assessed using the chi-square test for the categorical variables and Student's *t* or Mann-Whitney *U* test (also called Wilcoxon rank-sum test) for the continuous variables, as appropriate. The limitation of including one variable for every 10 events was considered.

The variables *older adult* (≥ 65 years), *leukocytosis* (WBC ≥ 10,000/mm³), *prolonged QTc* (≥ 440 ms) and *high creatinine level* (≥ 1 mg/dl) were created based on the observations of their relationship with de novo heart disease log-odds.

Then, a simple logistic regression was conducted with each selected variable (cardiovascular complication with hospitalization, sex, body mass index, older adult, hypertension, diabetes, COPD, severity, days in the hospital, prolonged QTc, leukocytosis, high creatinine level, C-reactive protein [CRP], urea, hematocrit below 40 %). The variables were individually included in the multivariate model (those with *p* value < 0.20 in the univariate model were selected), and their permanence was decided based on the Wald test (*p* < 0.05) and confusing effect on other variables (confusing means that causes variation to the OR of another variable > 20%). Since the aim was to build a predictor model of de novo heat disease, its parsimonious nature was prioritized.

The final model showed that intra-COVID-19 cardiovascular complications, COPD, QTc ≥ 440 ms in the EKG and leukocytosis (WBC ≥ 10,000 mm³) were independent predictors for developing de novo heart disease among post-COVID-19 patients with significant Wald test *p* value. A trend toward statistical significance was observed among patients aged ≥ 65 years and creatinine ≥ 1 mg/dl, which is considered clinically noteworthy since there is the possibility of lack of power because of the reduced sample size and the proximity of Wald test *p* value to the cut-off point. As to the weight of each variable, prolonged QTc showed the highest OR, followed by leukocytosis COPD, intra-COVID-19 cardiovascular complications, age ≥ 65 years and finally creatinine ≥ 1 mg/dl.

The model calibration was adequate, according to a non-significant Hosmer-Lemeshow test. The area under the curve (AUC) of the model was 0.77.

Results of other studies

A total of 18 Holter tests were conducted. Six patients developed complex ventricular arrhythmia already found in the basal EKG. Six patients evidenced ST in the EKG, and the Holter test showed additional mild supraventricular arrythmias or a normal tracing.

Nine patients underwent a magnetic resonance imaging (MRI), out of whom three evidenced findings compatible with myocarditis and six showed different unspecific alterations. Five patients underwent a cinecoronariography (CCG) and two of them were normal.

TABLES

Table 1. Demographic and anthropometric data
Age: 52 ± 13 years (median: 54) (range: 20-85)

	n (%)
Sex	
Male	128 (52)
Female	118 (48)
BMI	29.2 ± 5.7 (28.4)
Normal	59 (24)
Overweight	101 (41)
Obesity	87 (35)
Home country	
Argentine	142 (58)
Other	104 (42)
Ethnic group	
Caucasic	150 (61)
Amerindian	96 (39)

Table 2. History

	n (%)
Some history	175 (71)
Known heart disease	38 (15)
Chagas heart disease	9 (4)
Ischemic heart disease	4 (2)
Mitral valve prolapse – family history of mitral stenosis (MS)	1 (0.4)
Cardiomyopathy	12 (5)
Conduction disorders	9 (4)
Ventricular arrhythmia	8 (3)
Atrial fibrillation/flutter	6 (2)
Procedures	
Ablation	2 (1)
Electrical or pharmacologic cardioversion	4 (2)
Revascularization	1 (0.4)
Aortic valve replacement	3 (1)
Pacemaker or defibrillator	3 (1)
Other history	
Hypertension	63 (26)
Overweight	188 (76)
Diabetes	39 (16)
COPD/asthma	21 (8)
Others	107 (43)

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	n (%)
Number of risk factors	
0	130 (53)
1	79 (32)
2	27 (11)
3 or more	10 (4)
Medication	
Some medication	116 (47)
ACE inhibitors	53 (21)
Beta-blockers	22 (9)
Calcium channel blockers	9 (4)
Hypoglycemic agents	33 (13)
Statins	24 (10)
NSAIDs	9 (4)
Others	72 (29)
Vaccination (n: 193)	
None	127 (52)
Influenza	60 (24)
Pneumococcus	33 (13)
Both	29 (12)
Pre-infection symptoms	
None	199 (81)
Dyspnea	11 (4)
Precordialgia	3 (1)
Cough	7 (3)
Palpitations	6 (2)
Others	20 (8)
Prior EKC (37)	
Normal	10
Pathological	27
Prior functional class (FC)	
FC I	226 (92)
FC II	19 (8)
FC III	1 (0.4)

Table 3. Acute stage of COVID-19

	n (%)
Place	
Hospital	193 (78)
Home/hotel	53 (22)
Days in the hospital	16.5 ± 13 (13) (4-96)
Reason for hospitalization	
COVID-19	241 (98)
Guillain-Barré syndrome	1 (0.4)
Sustained ventricular tachycardia	1 (0.4)
Cerebrovascular accident (CVA)	1 (0.4)
Heart failure	2 (0.8)
Symptoms during COVID-19	
None	12 (5)
General symptoms*	168 (68)
Fever	154 (63)
Chest pain	27 (11)
Cough	125 (51)
Anosmia/ageusia	69 (28)
Gastrointestinal symptoms	40 (16)
Upper respiratory tract symptoms	13 (5)
Neurological symptoms	4 (2)
Odynophagia	34 (14)
Dyspnea	117 (48)
Palpitations	10 (4)
Precordialgia	12 (5)
Syncope	5 (2)
Cardiovascular complication during hospitalization	45 (18)
Arrhythmia	7 (4)
Shock	3 (1.5)
Increased troponin/creatinine phosphokinase (CPK)	29 (15)
Dilated ventricle	1 (0.5)
Severe hypertension	2 (1)
Heart failure	5 (2.5)
Pericarditis	1 (0.5)
Intra-COVID-19 pulmonary embolism (PE)	18 (7)
O_2 supply requirement	150 (61)
Admission to intensive care unit (ICU)	34 (14)
MV	20 (8)
HFOT	25 (10)

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	n (%)
Severity	
Mild COVID-19	91 (37)
Moderate COVID-19	96 (39)
Severe COVID-19	59 (24)

*General symptoms: asthenia, adynamia, inappetence, myalgia, arthralgia, malaise, headache

Post-COVID-19 examination

Table 4. Clinical interview

	n (%)
Days after discharge	62.8 ± 42 (47) (14-291)
≤ 30	30 (12)
31-60	124 (50)
61-90	43 (17)
> 91	45 (18)
Median – days	114
Symptoms	
None	58 (24)
Asthenia-adynamia	74 (30)
Myalgia-arthralgia	19 (8)
Sleep disorder	14 (6)
Chest pain	29 (12)
Potentially cardiovascular symptoms	108 (44)
Dyspnea	68 (28)
Palpitations	24 (10)
Precordialgia	24 (10)
Others	53 (22)
Neurological	26 (11)
Gastrointestinal	5 (2)
Psychological/cognitive	9 (4)
Cough	9 (4)
Symptomatic patients	
30 days after discharge	24/30 (80)
30-60 days after discharge	92/124 (74)
61-90 days after discharge	33/43 (77)
> 90 days after discharge	36/45 (80)

	n (%)
Current FC	
Same	130 (53)
Worse	116 (47)
FC II	64 (26)
FC III-IV	7 (3)
Medication	
None	110 (45)
ACE inhibitors	49 (20)
Beta-blockers	20 (8)
Calcium channel blockers	13 (5)
Hypoglycemic agents	27 (11)
Insulin	8 (3)
Statin	24 (10)
Anticoagulants	23 (9)
Diuretics	14 (6)
Corticosteroids	19 (8)
Bronchodilators	11 (4)
NSAIDs	21 (9)
Anticonvulsants	3 (1)
Others	35 (14)

Table 5. Physical examination

	X ± SD (median)
Sitting systolic blood pressure (mmHg)	134.8 ± 20 (133)
Sitting diastolic blood pressure (mmHg)	87.8 ± 13.9 (88)
Sitting HR (bpm)	79.6 ± 13.9 (78)
	n (%)
Sitting systolic blood pressure (mmHg)	
≤ 100	8 (3)
101-135	128 (52)
136-160	84 (34)
≥ 161	27 (11)
Sitting HR (bpm)	
< 60	7 (2)
60-90	182 (74)
≥ 90	59 (24)
Δ Sitting-standing systolic blood pressure	
Drop > 20 mmHg	12 (5)
Standing HR > 100 bpm	37 (15)

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	X ± SD (median)
Δ Sitting-standing HR	
Decrease or no change	54 (22)
Increase 0 ≤ 10 bpm	155 (63)
Increase 10-20 bpm	34 (14)
> 30 bpm	3 (1)
Signs of left-sided heart failure	10 (4)
Signs of right-sided heart failure	12 (5)
Cardiac auscultation	
Normal	211 (86)
Muffled heart sounds	5 (2)
Second heart sound (S2) splitting	2 (1)
Systolic murmur	27 (11)
Heart sound 4 (S4)	1 (0.4)
Pulmonary auscultation	
Normal	224 (91)
Rales	7 (3)
Wheezing	12 (5)
Hypoventilation	3 (1)

Table 6. EKG

	X ± SD (median)
HR (bpm)	77.7 ± 13.8 (75)
PR (ms)	155.3 ± 22 (160)
P (ms)	97 ± 17 (90)
QRS (ms)	81.2 ± 15 (80)
QT (ms)	363 ± 27 (358)
QTc (ms)	410 ± 27 (409)
QTd (ms)	38.5 ± 15.6 (40)
	n (%)
Sinus rhythm	243 (99)
Atrial fibrillation/fluffer, pace set by pacemaker	3 (1.2)
HR ≥ 100 bpm	27 (11)
HR ≥ 90	52 (21)
QRS ≥ 110 ms	12 (5)
AQRS < 0 degree	61 (25)
Q waves	10 (4)
R' in V1-V2	8 (3)
Early repolarization	1 (0.4)
Notched QRS	10 (4)
Poor R-wave progression	8 (3)
ST	
Ischemia	3 (3)
Secondary disorders	17 (7)
Unspecific disorders	34 (14)
QTc > 450 ms	19 (8)
Conduction disorders	32 (13)
Complete right bundle branch block (RBBB)	6 (2)
Complete RBBB + LAHB	3 (1)
Complete left bundle branch block (LBBB)	3 (1.2)
LAHB	17 (7)
AV (atrioventricular) block 1	2 (0.8)
AV block 2	1 (0.4)
Arrhythmias	50 (20)
Sinus tachycardia (> 100 bpm)	13 (5)
Sinus bradycardia	4 (2)
Supraventricular extrasystoly	5 (2)
Supraventricular tachycardia	2 (0.8)
Atrial fibrillation/fluffer	3 (1.2)
Ventricular extrasystoly	18 (7)

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Table 7. Lab tests

	X ± SD (median)
Hematocrit (%)	41.1 ± 4.3 (41)
White blood cells (mm³)	7,417 ± 1,964 (7,100)
Glycemia (mg/dl)	106 ± 27 (101)
Urea (mg/dl)	32 ± 12 (30)
Na+ (mmol/l)	140 ± 3 (140)
K+ (mmol/l)	4.3 ± 0.4 (4.3)
Creatinine (mg/dl)	0.8 ± 0.3 (0.8)
Total bilirubin (mg/dl)	0.6 ± 0.4 (0.5)
C-reactive protein (mg/dl)	0.7 ± 2.2 (0.3)
Pro-BNP (pg/ml)	54.8 ± 237 (10)
Troponin (ng/l)	6.8 ± 21 (3)
	n **(%)**
Hematocrit < 35	15 (6)
Leukocytes > 10,000	24 (10)
Glycemia > 110	66 (27)
Urea > 40	39 (16)
Creatinine > 1.1	20 (8)
Total bilirubin > 1.1	12 (5)
Elevated liver enzymes	24 (10)
CRP	
< 0.6	192 (78)
Elevated	51 (21)
> 1	27 (11)
Pro BNP	
< 10	119 (48)
10-100	118 (48)
> 100	10 (4)
Troponin	
< 3.2	177 (72)
3.2-18	47 (19)
> 18	18 (8)
Dimer D (n: 151)	
> 230 (ng/ml DDU)	57 (38)
> 400	30 (20)

Table 8. Echocardiogram (N: 223)

	X ± SD (median)
Left ventricle diastolic diameter	50.1 ± 8.3 (50)
Left ventricle systolic diameter	30.6 ± 5.2 (30)
Septum	9.4 ± 1.6 (9.5)
Left ventricle posterior wall	9 ± 1.5 (9)
Left atrium	39 ± 5.4 (39)
Aortic root	32.3 ± 4.3 (32)
EF assessed by Simpson's rule	61.9 ± 7.1 (63)
EF assessed by measurement of strain	56.8 ± 6.3 (57)
Right ventricle basal diameter	36.4 ± 4.5
Right ventricle median diameter	28.1 ± 5.3
Tricuspid annular plane systolic excursion (TAPSE)	23.3 ± 3.3
Pulmonary artery pressure	27 ± 8 (25)
Strain (n: 70)	-18.7 ± 3.2 (-19)
	n (%)
Left ventricle diastolic diameter > 54	42 (17)
Concentric hypertrophy	13 (5.2)
Septal hypertrophy	8 (3.3)
Left atrium dilation	93 (38)
Left ventricle function	
Normal	232 (94.3)
Mildly depressed	9 (3.7)
Moderately depressed	2 (0.9)
Severely depressed	2 (0.9)
Minor strain -18 % (n : 70)	20 (28)
Segmental wall motion abnormalities	5 (2)
Right ventricle dilation	42 (17)
Right ventricle depressed function	9 (3.6)
Mild pericardial effusion	4 (2)
Mild aortic stenosis	3 (1.5)
Critical aortic stenosis	1 (0.7)
Mild aortic insufficiency	44 (18)
Mild mitral stenosis	1 (0.7)
Mild mitral insufficiency	71 (29)
Moderate mitral insufficiency	11 (4.5)
Severe mitral insufficiency	2 (0.7)
Moderate tricuspid insufficiency	11 (4.5)
Mild pulmonary valvular insufficiency	22 (9)
Pulmonary artery pressure > 25 mmHg (96)	79 (32)
Pulmonary artery pressure > 30 mmHg (96)	32 (13)

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Table 9. Comparison between patients examined in the first and second wave

	Year 2020	Year 2021	p
Argentinian citizenship	63 (57 %)	79 (58 %)	0.89
Caucasian ethnic group	54 (49 %)	96 (70 %)	0.0007
Male sex	57 (52 %)	71 (52 %)	1
Normal BMI	25 (23 %)	33 (24 %)	0.88
Overweight	84 (76 %)	103 (76 %)	1
Prior medication	49 (44 %)	67 (49 %)	0.52
Prior heart disease	11 (10 %)	27 (20 %)	0.035
Number of risk factors			
0	58 (53 %)	72 (53 %)	1
1	35 (32 %)	44 (32 %)	1
2-4	17 (15 %)	20 (15 %)	1
Hospitalization	97 (88 %)	96 (70 %)	0.0001
Severity of COVID-19			
Mild	41 (37 %)	50 (37 %)	1
Moderate	34 (31 %)	62 (45 %)	0.02
Severe	35 (32 %)	24 (18 %)	0.01
O_2 supply requirement	64 (58 %)	86 (63 %)	0.43
MV requirement	12 (11 %)	8 (6 %)	0.16
Intra-COVID-19 cardiovascular complication	17 (15 %)	28 (20 %)	0.32
DNCFs	26 (24 %)	36 (26 %)	0.65