To Retest or Not to Retest the Experience of a Cardiology Emergency Clinic During the COVID-19 Pandemic

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Abstract

Acute cardiovascular pathology can frequently resemble the clinical and paraclinical picture of SARS-CoV-2 infection. The present paper aims to present the experience of a cardiology clinic during this pandemic and describe the way in which the clinical station was organized in order to limit in-hospital transmission of the virus. **Methods.** Patients admitted to an emergency cardiology department between May 1, 2020 and December 31, 2020 were retrospectively identified and divided into two groups: (1) those positive for SARS-CoV2 infection and (2) those with an initial negative test, but high suspicion for the infection, who were tested at least twice by RT-PCR. We followed the motivation for retesting as well as possible correlations between clinical and paraclinical parameters and the decision to retest. **Results.** A number of 334 patients were identified, 51 with a first positive RT-PCR test for SARS-CoV2 infection, and 276 who were tested for infection at least twice. The most common reasons for retesting were lung imaging and existence of subfever. The best predictive model for the outcome of the second RT-PCR test included the presence of lymphopenia, subpleural condensation, highest temperature during hospitalization, and the presence of at least two COVID-19 symptoms. **Conclusion.** The balance between prompt detection of patients with high suspicion of SARS-CoV2 infection (through PCR re-testing) and misuse of material resources should be guided by clinical algorithms.

Keywords

cardiovascular disease, emergency hospital, SARS-CoV-2, COVID-19

Rezumat

Patologia cardiovasculară acută se poate asemana frecvent cu tabloul clinic si paraclinic al infectiei SARS-CoV-2. Scopul lucrării este de a prezenta experiența unei clinci de cardiologie de urgență la debutul pandemiei COVID și a descrie organizarea acesteia pentru limitarea transmiterii nozocomiale a SARS-CoV-2. **Metode.** Studiu retrospectiv ce a inclus pacienții internați intr-o sectie de cardiologie de urgență în perioada 1.05.2020-31.12.2020, grupați în 2 loturi: (1) cei pozitivi pentru infecția SARS-CoV2 și (2) cei care au avut un prim test negativ si au fost testați de cel puțin două ori prin RT-PCR, suspiciunea pentru infecție fiind ridicată. S-a urmărit motivația retestarii, precum și posibilele corelații existente între parametrii clinici și paraclinici și decizia de retestare. **Rezultate.** Au fost identificați 334 pacienți, 51 pozitivi și 276 re-testați de cel puțin 2 ori. Cele mai frecvente motive pentru retestare au fost imagistica pulmonara și existența subfebrei. Cel mai bun model predictiv pentru rezultatul celui de-al doilea test RT-PCR a inclus prezența limfopeniei, condensarea subpleurală, cea mai ridicată temperatură în timpul spitalizării și prezența a cel puțin două simptome COVID-19. **Concluzii.** Balanța între detectarea promptă a pacienților cu suspiciune înalta de infecție SARS-CoV2 și utilizarea nejudicioasa a resurselor materiale ar trebui ghidată prin algoritm clinic.

Cuvinte cheie

boli cardiovasculare, spital de urgență, SARS-CoV-2, COVID-19

Introduction

Newly evolved coronaviruses pose a high threat to global public health. The current outbreak of COVID-19 is the third coronavirus outbreak in humans in the past two decades. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic that begun in December 2019 has affected more than 273 million people from over 200 countries, claiming over 5.3 million lives as of December 2021 [1]. SARS-CoV-2 affects multiple organs and systems, but severe forms are generated by involvement of the lungs and the cardiovascular system (the latter through myocardial injury, arrhythmias, acute coronary syndromes (ACS), and venous thromboembolism) [2]. Additionally, patients with pre-existing cardiovascular diseases are prone to severe complications from COVID-19 infection. Heart failure has been reported in 23% of in-hospital Chinese COVID-19 subjects [3]. Studies indicate overall prevalence of acute myocardial injury ranged from 5% to 38% depending on the criteria used [4].

Most common symptoms associated with COVID-19 are fever, cough, dyspnea, headache, and myalgia or fatigue. It was also found that the SARS-CoV-2-infected patients often have lymphocytopenia with or without leukocyte abnormalities [5].

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Biologically, there is a fairly common increase in cardiac biomarkers (such as high-sensitivity cardiac troponin, CKMB or NTproBNP) in those infected with SARS-CoV-2 [6]. Reports indicate that almost all COVID-19 patients with moderate or severe forms show elevated serum lactate dehydrogenase (LDH) levels [7]. Therefore, the clinical picture of the SARS-CoV-2 infection may sometimes overlap with the clinical picture of a patient with cardiovascular disease, making it particularly difficult to differentiate between the two.

We aimed to present the experience of a cardiology clinic during this pandemic and describe the way in which we organized our clinical station in order to limit in-hospital transmission of the virus. Hospitals can be a potential source of infection. We had to re-organize our clinic, in order to minimize patient contact with healthcare professionals, limit or reschedule hospital visits and outpatient clinics, and postpone non-urgent procedures, while still trying to maintain the clinical activity and the quality of the medical services, so that patients with cardiovascular diseases would not have to suffer.

Our purpose was to assess in an emergency cardiology clinic the positive cases of SARS-CoV-2 infection, the motivation to retest patients with an initially negative RT-PCR test, to find the possible correlations between clinical parameters and retest motivation and to compare retested patients and positive patients.

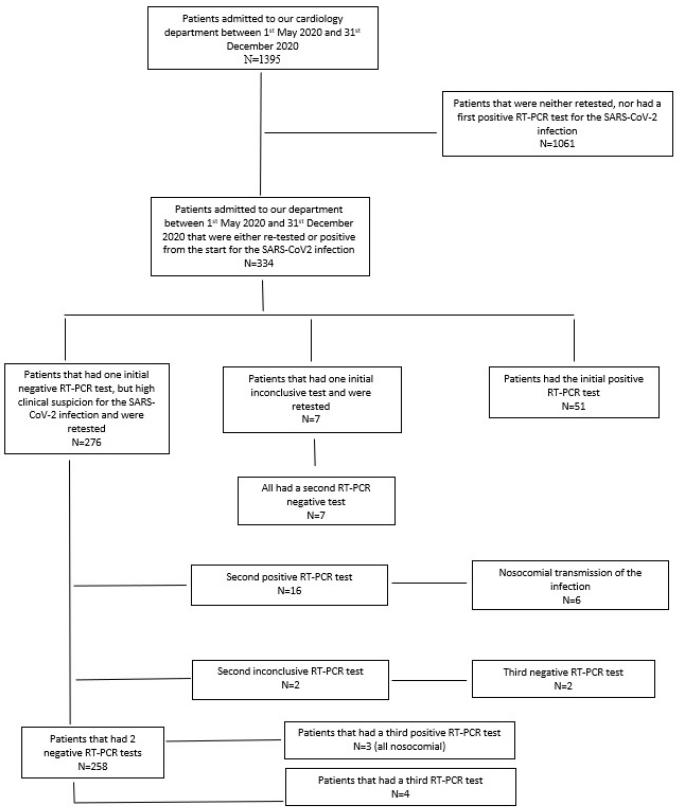


Figure 1 - Flowchart of the negative retested and the positive retested patients hospitalized in the Cardiology Unit between 1st May 2020 and 31st December 2020.

Material and Methods

1. Organization of our clinic.

We established well-defined circuits in order to isolate newly-admitted patients to our clinic from the negative patients (patients with at least one negative RT-PCR for the SARS-CoV-2 infection and no/low clinical suspicion for the infection). Upon admission, all patients were considered possible suspects for the SARS-CoV-2 infection and were isolated in separate hospital rooms until the results of the RT-PCR came back. In some cases, when the clinical suspicion was high, we decided to retest the patients, so that the in-hospital transmission of the virus would be kept as low as possible. Both the initial RT-PCR and the retest were processed from nasal and oropharyngeal swabs.

2. Study design.

We have retrospectively identified all patients hospitalized in the Cardiology Department of the Bucharest University Emergency Hospital between May 1, 2020 and December 31, 2020. We selected the positive patients for the SARS-CoV2 infection, as well as the patients who were tested at least twice by RT-PCR.

Patients were divided in two subgroups: patients positive for the SARS-CoV-2 infection and patients who were tested at least twice by RT-PCR for the infection, but with negative result (negative re-tested patients). (Figure 1)

For all patients, the following parameters were noted: demographic parameters, the existence of a contact with a positive case, the presence of symptoms suggestive of SARS-CoV2 infection, the cardiovascular diagnosis, the clinical state at the presentation of the patient, pulmonary imaging, the existence of another concomitant infection, the need for antibiotic administration, and the stated motivation for deciding retesting.

Clinical and demographic data: county of origin, age, gender, atrial and ventricular arrhythmias, the presence of atrioventricular block, bronchial rales, the presence of crackles at pulmonary auscultation, fever, low-grade fever, highest-temperature during hospitalization, arterial oxygen saturation (SaO2), cough, myalgia, dysphagia, ageusia, anosmia, dyspnea, digestive symptoms.

Conventional biological data: hemoglobin level at admission, number of leukocytes and the leukocyte formula at admission and at 48 hours, highest value of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and fibrinogen, ferritin, highest troponin I level, admission NTproBNP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), admission urea (BUN), admission creatinine, admission eGFR (estimated glomerular filtration rate), glycated hemoglobin (HbA1c), activated partial thromboplastin time (aPTT), creatine kinase (CK), creatine *kinase* myocardial band (CK-*MB*), Lactate dehydrogenase (LDH).

Echocardiographic data: significant valvular disease (more than moderate) and LVEF.

Pulmonary imaging: accentuation of the interstitial pattern, pulmonary condensation or alveolitis on the chest X-Ray, ground-glass image, its location and/or the presence of subpleural condensation on computed tomography. All images were analyzed

by the radiology department. ***Follow-up:*** we analyzed the motivation for retesting, the correlations between clinical and paraclinical parameters and the retest decision and compared these data between retested and positive patients.

3. Statistical analysis

We used an IBM SPSS Statistics Data Editor version 20.0. The variables with a continuous Gaussian distribution were expressed as mean ± standard deviation, while the discontinuous variables were expressed as absolute values or as a percentage. We used the t-test to compare the means of the values from two subgroups. The Pearson correlation coefficient was used for data with normal distribution. For the prediction analysis we used logistic regressions. We then used multiple regression to identify subsets of predictive factors. We also used **ROC curves (receiver operating characteristic curve**) to analyze and determine the performance of a classification model at all classification thresholds. Statistical significance was defined as a p-value <0.05.

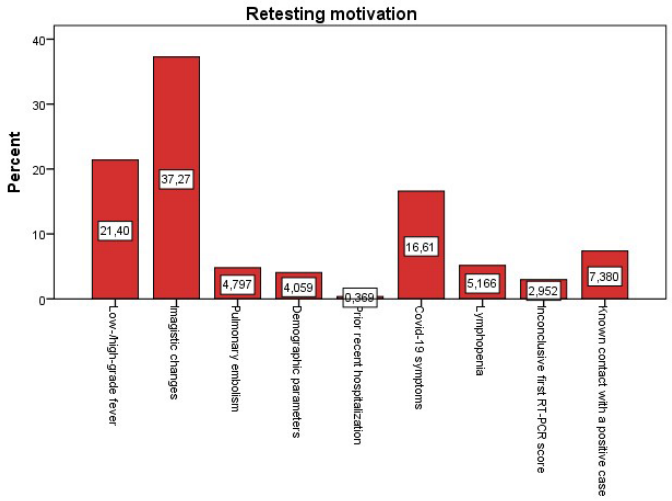


Figure 2 - Most important reasons for deciding RT-PCR retesting of patients, expressed in percent.

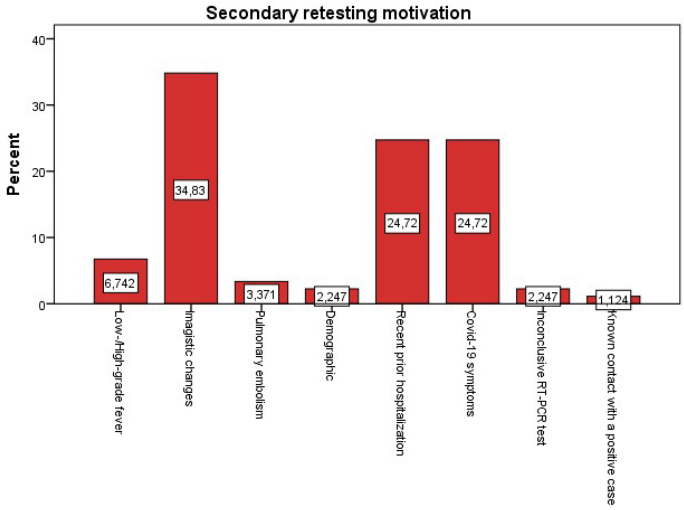


Figure 3 - Secondary most important for deciding RT-PCR retesting of patients, expressed in percent.

Results

We reviewed the records of 334 patients admitted to our department between May 1, 2020 and December 31, 2020 that were either retested or initially positive for the SARS-CoV2 infection. As many as 276 patients had one initial negative RT-PCR test, but the clinical suspicion for the SARS-CoV-2 infection was high so they were retested. A subgroup of 7 patients had one initial inconclusive test and were, therefore, retested (all of which were negative at the second test). A number of 51 patients had one initial positive RT-PCR test. Of the retested patients, 258 had a second negative RT-PCR test, 16 had a second positive RT-PCR test (of which six tested positive due to nosocomial spreading of the virus) and 2 had a second inconclusive tests. Both of the patients that had a second inconclusive RT-PCR test had a third negative test. Only three of the patients that had two negative RT-PCR tests had a third positive test, due to nosocomial spreading of the virus. Overall, from the 334 initial patients, 264 (79%) were negative, and 70 (21%) were positive (Figure 1).

Excluding the patients that became positive due to the nosocomial transmission of the disease, there were 276 patients with an initial negative RT-PCR test, of which 10 (3.6%) were positive at retesting.

Clinical, demographic, biological, and echocardiographic characteristics of all patients are presented in Table 1 and Table 2.

1. Reasons for re-testing

We identified the most frequent reasons for deciding to re-test patients with a high clinical suspicion for SARS-CoV-2 infection (Figure 2). These were: suggestive changes on the chest X-ray or CT (37.3%), followed by low- or high-grade persistent fever (21.4%) and typical symptoms for COVID-19 (16.6%). Of note, for most patients, there were at least 2 reasons for deciding to re-test (Figure 3). The most frequent secondary reasons for retesting were changes appearing on the chest X-ray or CT other than traits typical for COVID-19 (34.83%), typical symptoms for COVID-19 (24.7%), lymphopenia (24.7%), and/or low-/high-grade fever (6.74%).

2. Comparison between the SARS-CoV-2 positive patients and the re-tested patients

2.1 Demographic data

There were no statistically significant differences between the groups regarding demographic data (Table 1). Both groups were homed predominantly in the hospital's coverage area.

2.2 Contact with a confirmed positive case of SARS-CoV-2 infection

A total of 8.7% (27) patients from the entire study group had a known contact with a confirmed positive case of SARS-CoV-2

Table 1 - Comparison between demographic, electrocardiographic, echocardiographic, clinical and imagistic parameters in negative retested and positive patient.

Parameter		Negative patients	Positive patients	P value
Demographic data	Age mean (years)	65.07 ± 14.24	66.57 ± 13.12	0.42
	Age maximum (years)	92	95	NA
	Age minimum (years)	28	31	NA
	Gender	34.1% female, 65.9% male	40% female, 60% male	0.35
	Most frequent county of provenience	60.6% Bucharest (capital) 9.8% Giurgiu 7.6% Ilfov	58.5% Bucharest (capital) 8.6% Ilfov 7.1% Giurgiu	NA
ECG parameters	Atrial arrhythmias (%)	25%	35.7%	0.08
	Ventricular arrhythmias (%)	8.8%	7.1%	0.6
	Atrioventricular block	6.9%	10%	0.38
Echocardiographic parameters	Mitral regurgitation	36.04%	30%	0.008
	Mitral stenosis	0.7%	0	0.65
	Aortic regurgitation	7.06%	4.28%	0.15
	Aortic stenosis	8.83%	14.2%	0.56
	LVEF mean (%)	39.47 ± 12.46%	41.72 ± 15.37%	0.2
	LVEF reduced (<40%)	46.1%	37.5%	0.35
	LVEF mid-range (≥40%, <50%)	24.3%	27.5%	0.41
	LVEF preserved (≥50%)	29.6%	35%	0.18
Clinical parameters	Bronchial rales (%)	11.9%	11.4%	0.6
	Crackles (%)	31.8%	25.7%	0.29
	Low-grade fever (%)	25.7%	22.1%	0.54
	High-grade fever (%)	7.3%	18.6%	0.004
	Highest temperature during hospitalization (Celsius grades)	36.67 ± 2.79	37.47 ± 0.78	0.15
	SaO2 (arterial oxygen saturation) (%)	93.95 ± 13.48	95.16 ± 3.47	0.56
	Cough (%)	34.8%	54.3%	0.003
	Myalgia (%)	1.5%	8.6%	0.002
	Dysphagia (%)	1.5%	1.4%	0.6
	Ageusia/Anosmia (%)	0.4%	1.4%	0.72
	Dyspnea (%)	54.5%	59.4%	0.47
	Digestive symptoms (nausea, vomiting, diarrhea) (%)	1.1%	2.9%	0.29
Pulmonary imaging	Accentuation of the interstitial pattern on chest X-ray (%)	75.8%	81.4%	0.2
	Pulmonary condensation or alveolitis on the chest X-Ray (%)	48.1%	44.3%	0.49
	Ground-glass image on thoracic CT scan (%)	6.4%	11.4%	0.06
	Subpleural condensation on thoracic CT scan (%)	3.8%	10%	0.022

infection (including patients with nosocomial acquired infection). Of those, 18 tested positive at any point during hospitalization, the other 11 remained negative at re-testing.

2.3 Admission diagnosis

The most frequent diagnosis at admission was, as expected, acute coronary syndrome (54%), followed by acute cardiac failure (30.8%), pulmonary embolism (6.1%) and high-grade atrioventricular block (6.5%).

Similar percentages were found in the negative retested-patients group (n=264), 56.8% (150) being admitted for acute coronary syndromes, 22.7% (60) for acute heart failure, 9.1% (24) for pulmonary embolism, 6.8% (18) for high-grade atrioventricular block, 3.0% (8) for endocarditis, 1.1% (3) for deep vein thrombosis, and 0.4% (1) for myocarditis.

Of the positive patients (n=70), 45.7% (32) were admitted for acute coronary syndromes, 17.1% (12) for acute heart failure, 11.4% (8) for pulmonary embolism, 10% (7) for deep vein thrombosis, 10%

Table 2 - Comparison between biological parameters in negative retested patients and positive patients.

Parameter	Negative patients (mean ± standard deviation)	Positive patients (mean ± standard deviation)	P value
Admission hemoglobin level(g/dl)	13.62 ± 9.16	12.66 ± 2.35	0.4
Leukocytes at admission (x10³/µl)	11.10 ± 4.53	10.54 ± 7.05	0.43
Neutrophils at admission (percent) (%)	73.73 ± 12.08	73.34 ± 11.16	0.81
Neutrophils at admission (absolute value) (x10³/µl)	8.71 ± 5.94	7.25 ± 2.97	0.055
Lymphocyte at admission (percent) (%)	15.81 ± 8.62	16.36 ± 8.78	0.57
Lymphocyte at admission (absolute value) (x10³/µl)	1.58 ± 0.88	1.5 ± 0.82	0.54
Monocyte at admission (percent) (%)	9.07 ± 8.12	8.7 ± 3.62	0.711
Monocyte at admission (absolute value) (x10³/µl)	0.93 ± 0.65	0.91 ± 0.77	0.77
Leukocytes at 48h (x10³/µl)	9.59 ± 3.42	9.65 ± 3.43	0.92
Neutrophils at 48h (percent) (%)	69.64 ± 10.17	71.48 ± 11.89	0.29
Neutrophils at 48h (absolute value) (x10³/µl)	7.12 ± 5.17	7.13 ± 3.03	0.99
Lymphocyte at 48h (percent) (%)	18.22 ± 8.07	19.08 ± 12.97	0.57
Lymphocyte at 48h (absolute value) (x10³/µl)	2.11 ± 3.59	1.59 ± 1.03	0.34
Monocyte at 48h (percent) (%)	9.62 ± 3.02	8.66 ± 3.26	0.06
Monocyte at 48h (absolute value) (x10³/µl)	0.97 ± 0.91	0.84 ± 0.43	0.34
Highest Erythrocyte sedimentation rate (ESR) (mm/h)	31.07 ± 23.86	38.5 ± 23.74	0.042
Highest C-reactive protein (CRP) (mg/dl)	8.12 ± 9.24	12.21 ± 14.35	0.008
Highest Fibrinogen (mg/dl)	435.44 ± 160.71	448.44 ± 154.27	0.55
Ferritin (ug/L)	309.49 ± 435.33	377.22 ± 326.46	0.371
Highest Troponin I (ng/ml)	4647.97 ± 11089.05	2899.12 ± 5963.79	0.31
Admission NTproBNP (pg/ml)	4105.78 ± 7968.38	2623.6 ± 3993.31	0.27
Admission aspartate aminotransferase (AST) (mg/dl)	109.5 ± 335.36	55.24 ± 69.03	0.18
Admission alanine aminotransferase (ALT) (mg/dl)	68.2 ± 144.47	62.3 ± 134.07	0.76
Admission urea (BUN) (mg/dl)	57.66 ± 40.75	58.77 ± 40.28	0.84
Admission creatinine (mg/dl)	1.33 ± 1.23	1.59 ± 1.8	0.17
Admission eGFR (estimated glomerular filtration rate) (ml/min)	69.27 ± 30.78	66.11 ± 32.06	0.45
Glycated hemoglobin (HbA1c) (%)	6.59 ± 3.98	6.61 ± 1.18	0.97
Admission activated partial thromboplastin time (aPTT) (s)	36.65 ± 25.43	35.75 ± 15.78	0.78
Admission creatine kinase (CK) (U/L)	567.37 ± 1094.96	307.16 ± 530.52	0.06
Admission creatine kinase myocardial band (CK-MB) (U/L)	69.56 ± 132.41	26.85 ± 36.74	0.011
Admission lactate dehydrogenase (LDH) (U/L)	428.87 ± 420.59	320.05 ± 133.26	0.129

(7) for high-grade atrioventricular block, 2.9% (2) for endocarditis, and 2.9% (2) for myocarditis (Figure 4).

2.4 Echocardiographic parameters

As much as 75.6% (n=214) of the patients in the negative retest group and 72.8% (n=51) of the positive group had a LVEF<55%.

When analyzing the prevalence of moderate and severe valvular diseases, 8.8% (25) of the retested-patients had aortic stenosis, 7.1% (20) had aortic regurgitation, 0.7% (2) mitral stenosis, and 36% (102) had mitral regurgitation. In the positive-patients subgroup, 14.2% (10) had moderate or severe aortic stenosis, 4.3% (3) had moderate aortic regurgitation, 30% (21) had moderate or severe mitral regurgitation, and none had significant mitral stenosis (Table 1).

2.5 Arrhythmias

A higher percent of the positive patients than the negative retested patients had atrial arrhythmias (35.7% vs. 26.1%, p>0.05). There were no significant differences regarding the occurrence of ventricular arrhythmias between the two subgroups (7.1% in the positive patients, 8.5% in the retested patients, p>0.05) (Table 1).

2.6 Symptoms suggestive for Covid-19

As expected, a higher percent of the positive patients experienced symptoms suggestive of the SARS-CoV-2 infection than the negative-retested patients (60% vs. 33.7%, p<0.001).

The most frequent symptoms were dyspnea, low- (in the retested patients group) or high- (in the positive patients group) grade fever, and dry cough. Positive patients also presented with dysphagia, odynophagia and some even with ageusia and anosmia.

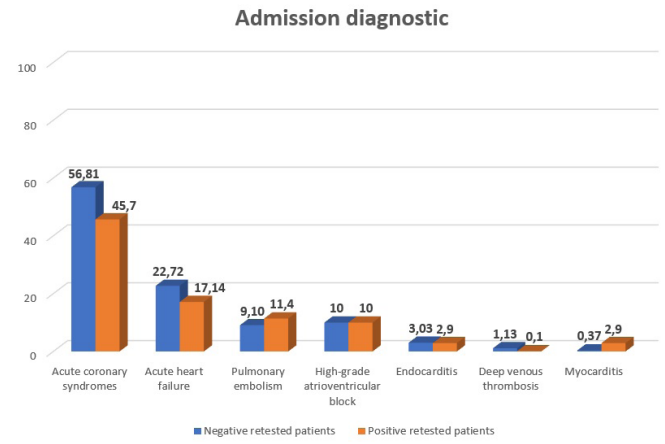


Figure 4 - Comparison between admission diagnostic in negative-retested and positive patients, expressed in percent from the entire lots.

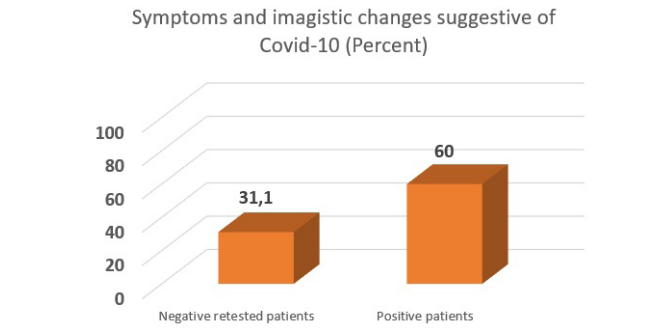


Figure 5 - Patients exhibiting both symptoms and imagistic changes on Chest X-ray or thoracic CT-scan, expressed in percent (comparison between negative-retested and positive patients).

A significantly higher percent of the positive patients had high-grade fever (18.6% vs. 7.3%, p=0.004), dry cough (54.3% vs. 34.8%, p=0.003), and myalgia (8.6% vs. 1.5%, p=0.002) (Table 1).

Also, more positive patients described dyspnea at admission (58.6% vs. 54.5%, but p>0.05) (Table 1).

2.7 Physical examination

Regarding physical examination, there were no significant differences in the presence of bronchial or alveolar rales or between the oxygen saturation at admission between the positive and the negative retested patients (Table 1).

2.8 Concomitant infections

A total of 65.7% of the positive patients received antibiotic treatment and 39% of the negative retested patients had other bacterial infections, such as urinary tract infections with E. Coli or Providencia spp., pulmonary infections with Pseudomonas spp., or Klebsiella pneumoniae or endocarditis, requiring antibiotic administration.

2.9 Biological parameters

Biologically, statistically significant differences between the negative retested patients and the positive patients concerned inflammatory parameters, such as C-reactive protein (for negative patients 8.1 ± 9.2 mg/dl vs. 12.2 ± 14.4 mg/dl for the positive ones, p=0.008) and ESR (31.1 ± 23.9 mm/h for negative-patients vs. 38.5 ± 23.7 mm/h for positive patients, p=0.04) and CKMB (mean values 69.6 ± 132.4 U/L for negative-patients vs. 26.9 ± 36.7 U/L for positive-patients, p=0.011).

We found no statistically significant differences between the two subgroups for NTproBNP and high-sensitivity Troponin I, although the negative retested patients had higher values of the two biomarkers (Table 2).

2.10 Pulmonary imaging

In the positive-patients subgroup, 81.4% (57) had an increase of the interstitial pattern and 44.3% (31) had alveolitis images on the chest X-ray. Only 15 of the 70 positive patients received a thoracic CT scan. Of those, 11.4% (8) had ground-glass images and 10% (7) subpleural condensation.

Of the negative retested patients, 75.8% (200) had accentuation of the interstitial pattern, whereas 48.1% (127), had alveolitis images on the chest X-ray. 61 patients had a thoracic CT, of which 6.4% (17) had ground-glass images and 3.8% (10) had subpleural condensation (Table 1).

As expected, a higher percentage in the positive patients group exhibited both typical COVID-19 symptoms (at least two symptoms) as well as pulmonary imaging changes compatible with the disease (60% vs. 31.1% in the negative retested group) (Figure 5). One positive patient and six negative patients had ground-glass images on the thoracic CT scan but no symptoms.

2.11 Correlations between re-testing reasons and other parameters

We tried to identify correlations between the most important retesting reasons, clinical and paraclinical parameters, and the results of the first, second, and third RT-PCR tests, but those were weak.

By multiple regression analysis, the best predictive model for the result of the second RT-PCR test included the presence of lymphopenia, subpleural condensation, and accentuation of the interstitial pattern and alveolitis images, the highest temperature during hospitalization and the presence of at least two different COVID-19 symptoms (from the ones counted above) (R=0.828, R^2=0.686, p=0.014) (Table 3). The same parameters didn't reach statistical significance for the first RT-PCR test. The patients who had a third RT-PCR test was too small for predictive models to have statistical power. The regressions that included inflammation markers (ESR, fibrinogen, and C-reactive protein) did not reach statistical significance.

We also plotted ROC curves in order to assess the predictive value and accuracy of different parameters. The presence of both symptoms and imagistic changes had a moderate predictive power for the result of the first RT-PCR test (AUC=0.626, CI 0.542-0.710) and the second RT-PCR test (AUC=0.683, CI 0.548-0.817) but was better than the presence of lymphopenia (AUC=0.527, CI 0.438-0.616 for the first RT-PCR test and AUC=0.563, CI 0.412-0.713 for the second RT-PCR test) (Figure 6).

Table 3 - Multiple regression analysis for the result of the second RT-PCR test (positive/negative).

	Pearson Coefficient of Correlation (R)	Coefficient of determination (R^2)	P value	Odds Ratio (OR)
Predictive model*	**0.828**	**0.686**	**0.014**	**1.035**

*Parameters included in the model: lymphopenia, subpleural condensation, accentuation of the interstitial pattern and alveolitis images, the highest temperature during hospitalization and the presence of at least two different COVID-19 symptoms

Ferritin at admission (AUC=0.648, CI 0.551-0.746 for the first RT-PCR test, for a value >172 ug/L with a sensitivity of 71% and a specificity of 55.5%; AUC=0.618, CI 0.464-0.771 for the result of the second RT-PCR test, for a value >162.5 ug/L with a sensitivity of 77.8% and a specificity of 56.1%) and the maximum temperature during hospitalization (AUC=0.680, CI 0.533-0.827 for the result of the first RT-PCR test, for a value >37.3 Celsius grades with a sensitivity of 75% and a specificity of 66.2%, AUC=0.862, CI 0.795-0.929 for the second RT-PCR test, for a value >37.5 Celsius grades with a sensitivity of 100% and a specificity of 76.8%) also had a moderate predictive power (Figure 6).

Discussion

The clinical picture of the SARS-CoV-2 infection can sometimes resemble that of a cardiovascular disease. Not only can the novel virus affect the heart and the vessels, it can also produce clinical and biological manifestations that can mimic cardiovascular illnesses unrelated to the infection. Therefore, it is often difficult to discern between the two pathologies. The increase in cardiac biomarkers (NTproBNP, high sensitivity cardiac troponin, CKMB, etc.) has been associated with the severity of the disease and predicted in-hospital mortality [6]. Studies show that the viral load peaks at around five to six days following the onset of symptoms, this being the moment when the RT-PCR test has most chances to be positive [8]. The diagnostic sensitivity of RT-PCR testing is highly variable, ranging in studies from 70 to 90% [9]. Even with sensitivity values as high as 90%, the effect of one false-negative test on in-hospital transmission of the infection would be exponential [10]. A sensitivity of 90% would mean that from 1000 patients admitted to a hospital, 100 would have false-negative RT-PCR tests.

It is also important to note that sample collection, handling, and transport might directly impact an assay's sensitivity [11]. In addition, significant temporal variability of viral shedding for oropharyngeal samples have been noted [8]. In short, a negative RT-PCR nasopharyngeal swab test is insufficient to rule out COVID-19. Thus, over-reliance on the results of the test may be dangerous.

Chest CT is a good diagnostic tool for detecting viral pneumonia. The sensitivity of chest CT is superior to that of X-ray. Early manifestations of COVID-19 might not be evident on chest X-ray, but chest CT abnormalities associated with COVID-19 have been observed even in asymptomatic patients [12].

Current guidance from the World Health Organization (WHO) and others calls for repeat testing (including sampling of the lower respiratory tract) in individuals who continue to display symptoms of COVID-19 [13].

Ai et al. (2020), Li et al. (2020) and Long et al. (2020) described dynamic conversions of RT-PCR results (negative to positive, positive to negative) for patients with repeated RT-PCR tests. All these studies recommend repeating RT-PCR to avoid misdiagnosis and emphasized the helpfulness of chest CT scans in patients with a high clinical probability of COVID-19 infection but with an initial negative RT-PCR test [14]. Moreover, the possibility of patients being in the incubation period at admission and becoming positive during hospitalization remains plausible.

Kucirka et al. found that the median false-negative rate on the day of symptom onset was 38% but decreased to 21% after three days [15]. Another recent study estimated that the false negative rate at symptom onset is 23.8%, but the probability of two false negatives is as low as 5.7% and thus advocated for repeat RT-PCR testing [16]. Still, a study conducted in the USA suggested that negative predictive value did not increase with repeated RT-PCR testing [17].

Patients admitted for cardiovascular emergencies, like the ones admitted to our clinic, can frequently present with symptoms and imaging changes similar to those described in the SARS-CoV-2 infection. Moreover, many of the chronic cardiovascular pathologies can be precipitated by the presence of infection. It is therefore justified to be skeptical towards the result of one RT-PCR test when the clinical suspicion is high. In addition, clinics like ours with a high-influx of patients can become epicenters of the pandemic, due to nosocomial transmission of the disease, if there if not enough attention given to the possibility of false-negative RT-PCR results.

However, being an emergency clinic implies the fact that the turnover of patients must be fast in order to be able to accommodate an appropriate number of patients presenting with cardiovascular emergencies. Almost half of the patients-rooms in our clinic have been transformed in isolation-rooms, so that patients are isolated while waiting for the results of their RT-PCR tests and concomitantly receiving treatment for their cardiovascular diseases. This means that there is a limited number of patients that can be retested at a certain time in order to not block all the available places in the clinic. Hence, a rigorous algorithm for deciding to retest patients would be much needed.

Another problem that must be taken into consideration is the fact that some patients stay in the emergency department for a relative long period of time (because they require mechanical ventilation for a period of time, because there are no available places, etc.), which makes them more prone to acquire the SARS-CoV-2 infection. But those patients would most probably have an initial negative RT-PCR test and become positive during hospitalization. The number of those patients is directly proportional to the incidence of the disease at a certain time. Therefore, it is not possible to isolate all of them for

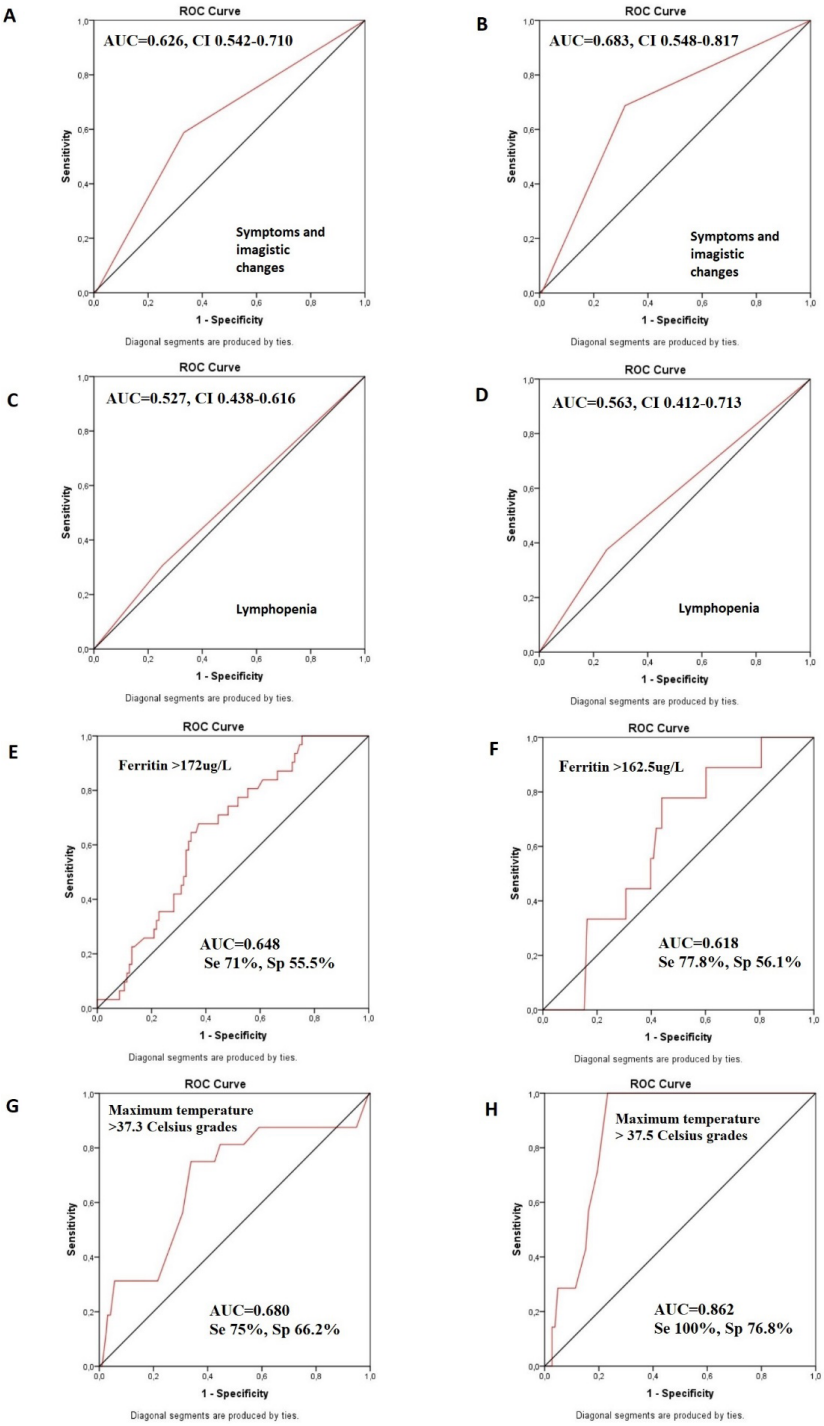


Figure 6 - ROC curves for different parameters and the result of the first and second RT-PCR test. Panel A- ROC curve for the concomitant presence of both Covid-19 suggestive symptoms and imagistic changes and the result of the first RT-PCR test (AUC=0.626, CI 0.542-0.710), Panel B- ROC curve for the concomitant presence of both Covid-19 suggestive symptoms and imagistic changes and the result of the second RT-PCR test (AUC=0.683, CI 0.548-0.817), Panel C- ROC curve for the presence of lymphopenia at admission and the result of the first RT-PCR test (AUC=0.527, CI 0.438-0.616), Panel D- ROC curve for the presence of lymphopenia at admission and the result of the second RT-PCR test (AUC=0.563, CI 0.412-0.713), Panel E- ROC curve for the value of ferritin at admission and the result of the first RT-PCR test (for a value >172ug/L, a sensitivity of 71% and a specificity of 55.5%, AUC=0.648, CI 0.551-0.746), Panel F- ROC curve for the value of ferritin at admission and the result of the second RT-PCR test (for a value >162.5ug/L, a sensitivity of 77.8% and a specificity of 56.1%, AUC=0.618, CI 0.464-0.771), Panel G- ROC curve for the maximum temperature during hospitalization and the result of the first RT-PCR test (for a value >37.3 Celsius grades, a sensitivity of 75% and a specificity of 66.2%, AUC=0.680, CI 0.533-0.827), Panel H- ROC curve for the maximum temperature during hospitalization and the result of the second RT-PCR test (for a value >37.5 Celsius grades, a sensitivity of 100% and a specificity of 76.8%, AUC=0.862, CI 0.795-0.929), Se- sensitivity, Sp-specificity.

the entire duration of their hospitalization. This highlights once more the need for clinical algorithms to help us decide the probability of a patient becoming positive.

On the other hand, a large amount of testing may increase the number of false positive tests and cause the significant expenditure of resources unnecessarily. However, due to the high specificity of the RT-PCR tests, the false-positive rate is estimated to be relatively low (0.8–4%) [14].

From our experience, there were no patients with false-positive RT-PCR tests, as all the patients who tested positive at any point during hospitalization had symptoms suggestive of the disease and/or imagistic changes.

Concerning the imaging changes present in this disease, one study showed that the diagnostic accuracy of the chest CT suggesting COVID-19 was 71%. Moreover, CT chest scan has a high negative predictive value for this infection [12]. However, chest CT cannot be performed on all patients as a screening method, in order to rule out the SARS-CoV-2 infection. In addition, CT scan cannot differentiate between different viral etiologies, and the cost of a CT scan is higher than that of a RT-PCR, and its availability much lower.

From our experience, 3.6% of the admitted patients had a false-negative first RT-PCR test (they were positive at retesting). This might not seem as a very high percentage, but in fact, this means that the methods we used in order to limit the in-hospital spread of the virus, as well as the retesting reasons, helped avoid the nosocomial spread, which could have been exponential taking into account the infectiousness of the circulating strains.

A higher percent of the positive-patients had a known contact with another already known positive case, but many of the patients did not know or confess this upon admission.

The percentage of patients with a certain admission diagnosis were relatively similar in the two study groups, with the exception of deep vein thrombosis, which was more prevalent in positive patients, confirming the hypothesis that SARS-CoV-2 infection is thrombogenic.

As expected more positive patients experienced symptoms suggestive of the SARS-CoV-2 infection than the negative-retested patients. Positive patients presented more frequently with high-grade fever, cough, and myalgia. Therefore, paying attention to the presence of specific symptoms is valuable when deciding retesting of patients. Of note, 39% of the negative retested patients had other bacterial infections, which might explain some symptoms, as well as the biological changes.

In accordance with current literature, the positive patients had higher C-reactive protein and ESR values. The higher CKMB values in the negative retested patients subgroup could be explained by the larger number of patients admitted with acute coronary syndromes in this subgroup.

There was a higher percent of the positive-patients that had subpleural condensation on the thoracic CT scan, which points towards a degree of specificity of this imagistic change for the disease.

Also, a higher percentage from the positive patients exhibited both typical symptoms for COVID-19, as well as pulmonary imaging changes compatible with the disease which suggests that an appropriate algorithm for deciding retesting of patients should include both clinical and imaging parameters.

A recent multi-center retrospective study found that a model that accounted for higher age, vital sign abnormalities, and lower white blood cell count could serve as a strong predictor for COVID-19 positivity in patients with one initial negative RT-PCR test. The most important variables in the logistic regression, were higher age, lower initial oxygen saturation, higher initial temperature, and lower white blood cell count [18]. In our case, the correlations between clinical and paraclinical parameters and the results of the first, second, and third RT-PCR tests were weak. The best predictive model for the result of the second RT-PCR test included the presence of lymphopenia, subpleural condensation, accentuation of the interstitial pattern and alveolitis images, the highest temperature during hospitalization, and the presence of at least two different COVID-19 symptoms.

The optimal interval to repeat testing is a matter of debate, different studies suggesting a range from one to six days following the first negative test. A study conducted in Wuhan, showed that performing three RT-PCR tests for diagnosing and discharging people with COVID-19 instead of just two tests, reduced the estimated total number of symptomatic cases from 51,144 to 45,013 in 43 days. The former strategy also led to 850.1 quality-adjusted life years (QALYs) of health gain, 749.4 QALYs being attributable to years of life saved [19]. This study shows that, accounting for the moderate rate of detection of the tests, it is justified in regions where the number of cases is high to intensify the number of diagnostic tests. However, we must keep in mind the economic burden, the human resources, and the time required when deciding to retest too many patients.

Study Limitations

The major limitation of this study is the retrospective nature and its consequently evaluation of the patients. Moreover, the patient group that had a third RT-PCR test was too small for predictive models to have statistical power.

Conclusions

The novel coronavirus, its fast propagation, and its unpredictable effects on the human body imposed a burden on the health systems worldwide. The pandemic led to the mobilization of the entire medical world in order to study the mechanisms of action of the virus, reduce contagion, and treat the disease. Hence, in order to limit the spread of the virus, it is legitimate to retest patients when the clinical suspicion for the SARS-CoV-2 infection in high.

Overall, in our experience and for the studied interval, the percent of nosocomial transmission of the disease was very low. This study advocates for retesting patients when clinical suspicion is high. The best algorithm for deciding retesting is still to be determined, but some of the useful guiding parameters are indicated in this article.

There is a definite need for more sensitive and specific tests or combinations of tests to minimize the risk of false-negative tests and the risk of in-hospital transmission of the virus.

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Competing interests

None declared.

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