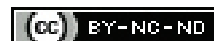# Implementation of Good Clinical Practice in Early COVID-19 Pandemic

CONSTANTIN TUDOR LUCA[1], SVETLANA MOŞTEORU[2], LAURENCE SPERLING[3], ALINA GABRIELA NEGRU[4], DANIELA MAXIMOV[5], ADINA BUCUR[6], SIMINA CRIŞAN[7], DAN GAIŢĂ[8]

ABSTRACT

Introduction: The novel Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has spread across the globe generating a pandemic. Every affected country has tried its best to mitigate the virus effects.

Aim: This study was designed to implement the good clinical practice in the Institute of Cardiovascular Diseases Timişoara (ICDT) for Coronavirus Disease-2019 (COVID-19) infection by a retrospective search for patients with a possible COVID-19 infection before widespread testing was available in our country.

Materials and Methods: The retrospective study was conducted on selected group of 19 patients admitted to the ICDT, who displayed radiological signs of possible SARS-CoV-2 infection, between September 2019 to May 2020 in collaboration with the Radiology Department. Patients have been followed-up regarding their clinical status and asked to participate in Immunoglobulin G (IgG) antibody testing at a local laboratory. The patients were divided based on the period they were admitted to the hospital into four groups: September-December 2019, January-February 2020, March-April 2020 and May 2020. The patients tested for coronavirus came from all four timeframes.

Results: Only 13 patients (male: female ratio was 10:3; mean age was 71.69 years) from the initial group were available and willing to answer a short interview and only five agreed to be tested for SARS-CoV-2 IgG antibodies. Most of the patients admitted to the hospital were suffering from acute myocardial infarction (30.76%), as well as heart failure (30.76%), followed by coronary heart disease (15.38%). A 30.7% of the patients had atrial fibrillation, 23.1% were also diagnosed with pneumonia during their hospital admission, 23.1% were also being treated for arterial hypertension, 7.69% had diabetes mellitus and Chronic Obstructive Pulmonary Diseases (COPD). Out of the five patients tested for IgG antibodies, two tested positive, with a titre above 1.4.

Conclusion: The patients who have gone through the SARS-CoV-2 infection without being previously diagnosed were identified and followed-up on their health status. By conceiving and performing this study, the authors have strived to establish a new set of rules to advance and improve good clinical practice in unprecedented times.

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is 82% similar to previous SARS-CoV-2, which had infected globally 32 regions between 2002 and 2003 and more than 89% similar with two bat-SARS-CoV-2 like viruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, which were isolated from *Rhinolophus sinicus* in Zhoushan, China in 2015-17 [1]. The clinical signs of COVID-19 are similar to those caused by other coronaviruses such as SARS-CoV and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). These include flu-like symptoms of mild intensity in most cases. Still, approximately 20% of the cases become complicated with interstitial pneumonia and a variable degree of respiratory failure leading to Acute Respiratory Distress Syndrome (ARDS) and multiple organ failure [2]. Cardiac injury was observed among 23% of the most severely ill patients [3]. Most patients in China were between 40 and 60-year-old, but data from other parts of the world contradict this pattern. Also, data on Chinese patients have so far shown that diabetes, hypertension and cardiovascular diseases are the most prevalent co-morbidities in patients infected with SARS-CoV-2 and patients with severe health conditions are more prone to having a more unsatisfactory outcome, if infected [2,3].

The standards and guidelines for the clinical practice during the first months of the pandemic were rethought and restructured continuously, leaving a large margin of variability between the protocols used in different countries and regions [4]. In June 2020, the European Society of Cardiology (ESC) provided a document with consensus value regarding the epidemiology, the intricated pathophysiology of SARS-CoV-2 and precipitating cardiovascular disease, strategies for diagnosis of SARS-CoV-2 and reorganisation of triage system to protect healthcare professionals and cardiovascular patients [5]. This study's relevance consists of concretising a central idea-finding ways to test and safely treat cardiovascular patients with pneumonia and the typical imaging aspect of ground glass at pulmonary Computed Tomography (CT) during the early pandemic. Other relevant aspects of this study are retrospectively identifying patients with SARS-CoV-2 pneumonia and establishing possible links between the infection and the cardiovascular diseases for which the patients were addressed from September 2019 to June 2020. Romania entered a lockdown at the end of March, stopping most commercial endeavours, closing schools and universities, in addition to ceasing all non vital activities, imposing curfews on its citizens. Since there were not enough mass testing resources at the beginning of the pandemic, patients were only tested following a strict case definition based on epidemiological criteria. The situation soon improved with the availability of widespread Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) testing and tests for detecting antibodies in patients exposed to the disease.

The authors designed the study retrospectively as early as possible (the patients being tested in the first days of June 2020) to discover if the virus had been circulating in Europe during early Autumn-Winter 2019/2020 based on suspicious radiological findings and to find any relation between the infection and the cardiovascular events, the patients were addressed for. The ICDT is a modern cardiovascular centre in West Romania that ensures high-quality

cardiovascular emergency management throughout the western part of the country, covering essential fields such as interventional cardiology, electrophysiology, cardiovascular surgery, prevention and rehabilitation. The study aimed to document the regional institute's experience in facing the COVID-19 pandemic while continuing high clinical care quality to ensure the best care for cardiovascular patients.

Other goals of this study were to avoid a waste of resources, develop protocols and procedures to identify patients at high risk of having SARS-CoV-2 infection, develop an optimal patient flow from hospital admission to discharge and adapt clinical practice in the setting of this unprecedented and challenging pandemic.

MATERIALS AND METHODS

The retrospective study was conducted in the Institute of Cardiovascular Diseases Timisoara (ICDT) from September 2019 to May 2020. The study received approval from the local hospital Ethics Committee (4081/23.06.2020) and the Helsinki Declaration.

This study aimed to discover patients admitted to ICDT for acute or chronic decompensated cardiovascular disease, potentially infected with COVID-19, before widespread testing was available in the country to trace infection since its starting. Nineteen consecutive patients were selected in collaboration with the Radiology Department, who displayed radiological signs of possible SARS-CoV-2 infection [6,7] based on current recommendations from the Radiological Society of North America endorsed by the Society of Thoracic Radiology and the American College of Radiology [8]. All patient charts were reviewed and analysed for the patient's infectious context, laboratory work, and clinical status. Patients were followed-up regarding their clinical status and were asked to participate in SARS-CoV-2 IgG antibody testing at a local laboratory. The tests were centralised during the subsequent scheduled cardiologic follow-up.

STATISTICAL ANALYSIS

All statistical analysis was performed using Microsoft Excel 365 through descriptive statistics (percentage, mean).

RESULTS

Total 19 patients initially deemed suitable to participate, upon investigation, out of which one patient died during the index hospitalisation due to cardiovascular causes (dilated cardiomyopathy), although he also had pneumonia. The remaining patients were contacted, but only 13 were available to answer the follow-up questions. Out of these, 5 agreed to be tested for SARS-CoV-2 IgG antibodies. The testing started in June 2020, shortly after the full availability of tests in Romania.

The male: female ratio among the thirteen patients was 10:3 and the mean age was 71.69 years. The patients were grouped based on the period they were admitted to the hospital:

- September-December 2019 (a time when the SARS-CoV-2 was not detected in Europe)
- January-February 2020 (the period when the first reports of the virus emerged in Europe)
- March-April 2020 (the time when the worldwide pandemic was declared and the beginning of the lockdown in Romania)
- May 2020 (the time when widespread testing became available in Romania).

There were five eligible patients in September-December 2019, four during the second period January-February 2020, three during the March-April 2020 timeframe and one in May 2020. The patients tested for coronavirus came from all four timeframes: two from September-December 2019, one from January-February 2020, two from March-April 2020 and one from May 2020 previously tested negative, refusing second testing.

Most of the patients were admitted with acute myocardial infarction (30.76%), as well as with heart failure (30.76%), followed by coronary heart disease (15.38%) [Table/Fig-1]. Total 30.7% of the patients either had paroxysmal atrial fibrillation with only one episode or persistent atrial fibrillation, 23.1% were also diagnosed with pneumonia during their hospital admission, 23.1% were also being treated for arterial hypertension, and 7.69% had diabetes mellitus and COPD [Table/Fig-2].

Presenting cardiac complications	n (%)
Myocardial infarction	4 (30.76%)
Heart failure	4 (30.76%)
Coronary heart disease	2 (15.38%)
Pulmonary thrombembolism	1 (7.69%)
Pericarditis	1 (7.69%)
Valve replacement	1 (7.69%)

[Table/Fig-1]: Primary diagnosis at admission (N=13).

Co-morbidities	n
Atrial fibrillation	4
Pneumonia	3
Arterial hypertension	3
Diabetes Mellitus	1
Chronic Obstructive Pulmonary Diseases (COPD)	1

[Table/Fig-2]: Main comorbidities found in the groups of patients.

Only two patients had a body temperature above 37.3°C and five had increased leucocytes counts; however, all had higher Erythrocyte Sedimentation Rate (ESR). Regarding other clinical signs of a respiratory infection, three patients (23.1%) had a persistent dry cough during their hospital admission. All of the patients had been admitted between March and April 2020. All patients showed radiological signs of various degrees of pneumonia on their chest x-ray.

Most patients recovered at home, having no other infection symptoms or other hospital admissions, but for one patient who needed two subsequent hospital admissions in the Pneumology ward. Five of the interviewed patients agreed to be tested for SARS-CoV-2 IgG antibodies and two (40%) tested positive, having an antibody titre above 1.4. These patients had been hospitalised in March 2020, one for myocardial infarction and one for acute heart failure, and had clinical signs of a respiratory infection. Also, both of them were admitted to the cardiac intensive care unit. Moreover, it is worth pointing out that one of them reported flu-like symptoms previously in January 2020. The antibody titre was also different between the two patients, one having 4.69 and the other 9.83. Finally, none of the patients had family members symptomatic for COVID-19 or who tested positive.

DISCUSSION

Ever since the publication in May 2020 of the short communication regarding the case of a 42-year-old male patient infected with SARS-CoV-2 in December 2019 in France, who had not travelled to China priorly [9], the scientific community has been in turmoil regarding the actual timeline of the COVID-19 pandemic and the possibility that the Chinese source of infection could have spread much earlier than previously known and at a community level, not only through travellers. The authors of this study started from the observation that the symptoms of a SARS-CoV-2 infection may be similar to the common flu, which affects yearly most countries, thus making it hard to suspect earlier a possible infection. That is why when designing the current study, the authors have taken into consideration the possibility that COVID-19 might have been present in Romania as well before the first confirmed case in February 2020. The period between September-December 2019 was included in

the research to cover the autumn-winter timeframe when upper respiratory tract infections are most common. However, the results showed no SARS-CoV-2 infections during the specified period.

Previous epidemics of SARS, MERS or influenza have shown that the extra-pulmonary effects have primarily been underestimated [10]. The effects of such viruses on the cardiovascular system have been documented, including myocarditis, acute myocardial infarction and exacerbation of heart failure [11,12]. Myocardial infarction and heart failure have been the primary reasons (30.76%) for the index suspect admitted to he hospital. The two confirmed cases have had a myocardial infarction and acute heart failure. Moreover, coronary plaque rupture in patients with coronary artery disease increases due to viremia-induced systemic inflammation [11,13]. It is worth mentioning that all the COVID-19 suspect patients had a high ESR, a marker of inflammation. One should also consider that systemic inflammation effects are pro-coagulant, which may increase the likelihood of stent thrombosis [13]. As a side note, we did indeed have a patient with stent thrombosis among the present study patients. A recently published study by Wang D et al., included arrhythmias among the clinical cardiac manifestations of COVID-19 infection [14]. The most common co-morbidity in the present study patients was atrial fibrillation (30.7%).

The long-time effects of pneumonia on the cardiovascular system are long-lasting, including the persistence of heightened systemic inflammatory and pro-coagulant activity and upto 10 years increased cardiovascular risk [15]. As far as the lipid metabolism is concerned, a metabolomic study on 25 SARS survivors showed a disruption in the lipids profile upto 12 years after clinical recovery from pneumonia [16]. The aim of conceiving and performing this study was to observe a new set of rules to improve good clinical practice in unprecedented times, advancing our approach further.

The first rule has been to acknowledge the errors: Although universal testing for SARS-CoV-2 for all patients admitted to ICDT should have been the gold standard ever since the debut of this pandemic, the scarcity of materials and testing facilities have made it somewhat demanding during the first several weeks, more so given the fact the national case definition for testing was restrictive at that time.

The second rule was to ask tough questions: Efforts have been made to uncover the exact number of patients who might have been potentially infected and gone undetected and to organise and evaluate our conduct and hospital circuits correctly.

The third rule was to make an efficient plan: Based on this, the study was devised to uncover potentially infected patients to evaluate further their health, potential complications that might appear in time, and investigate any potential further dissemination of the infection.

The fourth rule was to make it harder to make mistakes again: The current standard includes testing for SARS-CoV-2 for all symptomatic or asymptomatic patients admitted to ICDT. Therefore, any possible infected patient is revealed, and the rest of the patients as well as our healthcare professionals, are better protected.

The fifth rule was to communicate with others: By writing this paper, the authors attempt to disseminate the acquired experience and expertise with the novel coronavirus while constantly improving the methods to serve other healthcare institutions as an example.

A very recent study published in Nature in June 2020 tackles precisely the issue of antibodies by testing asymptomatic versus symptomatic COVID-19 positive patients and the results are somewhat worrisome because compared to SARS-CoV and MERS who provided immunity for atleast two years [17,18], the antibodies for SARS-CoV-2 appear to decrease after 2-3 months; whereas in asymptomatic patients, the antibody titre is insignificant to beginwith [19]. It would be of interest to retest our group of patients over time to see the changes in the IgG antibody titre, given that the two positive patients had significantly different titres.

Limitation(s)

One of the limitations is the small sample size, the fact that not all patients contacted for an antibody test agreed to participate and most of them preferred just the interview. Less than half of the patients contacted were tested for COVID-19. The scarcity of testing was caused by the fact that most of the patients were apprehensive of social contact, even if it meant a local laboratory of their choice and most of them wanted to keep social distancing. Secondly, the testing of choice, IgG antibodies against SARS-CoV-2, has the disadvantage that although it can detect that a patient has gone through infection, it cannot pinpoint the exact moment. Authors have had this issue with one patient who tested positive for IgG antibodies and has had two infectious episodes, one in January and another in March. It is hard to tell which one was the COVID-19 infection.

The antibodies for SARS-CoV-2 appear to decrease after 2-3 months, hence the present study patients over time should have been retested, to check for the changes in the IgG antibody titre, given that the two positive patients had significantly different titres.

CONCLUSION(S)

Several essential aspects can be learned from the present experience to guide for future course of COVID-19 pandemic and other potential epidemic or pandemic infectious diseases. That is why, it is essential that each medical facility learns from its mistakes and implements a set of clinical practices aimed at providing the best care for their patients while keeping patients and medical teams safe. By systematically and early testing of patients admitted in hospital, keeping the constant flow of admissions by organising the departments to provide care to both infected and non infected patients, discovering and following up the highest possible number of patients that have been infected before pandemic declaration, establishing the co-morbidities and the correct admission diagnosis of every patient, taking into account the potential implication of the infection in the genesis of the acute event and follow the potential long-term complications of the infectious disease. As therapies are constantly changing following the new data gained from the experience of providing care to these peculiar patients, it is imperative that all interested parties, from patients to healthcare professionals and scientists, work together to ensure a safe climate for everyone concerned.

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