Clinical characteristics and cardiovascular implications of the dead patients for COVID-19

Katia Falasca,1 Claudia Ucciferri,1,2 Alessandro Brandimarte,1 Antonio Auricchio,1 Michela Pontolillo,1 Luca Caiazzo1 and Jacopo Vecchiet1

Abstract
Coronavirus Disease 2019 (COVID-19) caused by 2019 novel coronavirus (named SARS-CoV-2), has become a global pandemic. Aged population with cardiovascular diseases is usually more susceptible to SARS-CoV-2 infection with an increased risk of severe complications and elevated case-fatality rate. Despite of several researches about COVID-19, cardiovascular implications related to this infection still remain largely unclear. The aim of this study is to evaluate the clinical characteristics of dead patients with COVID-19. We enrolled all patients with more than 50 years of age with laboratory confirmed COVID-19, admitted to infectious clinical diseases PO SS Annunziata of Chieti (Italy) from March 2020 to April 2020 who died during hospitalization. Demographics, underlying comorbidities, clinical symptoms and signs, laboratory results, computed tomography of the chest, treatment measures, and outcome data were collected. We enrolled eight patients, the age was 82 ± 9.7 years, four female and four male. All patients had comorbidity, such as hypertension (7 [87.5%]), diabetes (1 [12.5%]), and heart disease (6 [75%]). Common symptoms included fever [8 (100%)], dry cough (1 [12.5%]), and dyspnea (3 [37.5%]). All patients [8 (100%)] showed local and/or bilateral patchy shadowing on chest computed tomography that is the typical radiological finding in COVID-19. Lymphopenia was observed in seven patients (87.5%). All patients showed elevated troponin and prolongation of the QTc interval (p < 0.05). In this study we demonstrated that in SARS-CoV-2 infection, the deaths occurred in the non-ICU population with more than 50 years are related to cardiac causes. In our cases elongation of QTc and alteration in troponin are present in all patients who died and could represent a data to better stratify the population at risk. More detailed research on cardiovascular involvement in COVID-19 patients with sudden deaths showed a predictive role of troponin and QTc elongation.

Keywords
SARS COV2, dead, heart, mortality

Date received: 8 July 2020; accepted: 2 December 2020

Introduction
A new challenge has recently emerged for the healthcare community across the world: the infection caused by a novel coronavirus, officially known as SARS-CoV-2, responsible of a clinical condition called COVID-19. The clinical presentation of this pathology includes fever,
dry cough, fatigue, shortness of breath and acute respiratory distress syndrome (ARDS) that can lead to death of the infected patients.\(^1\) High infectivity, ability to be transmitted even during asymptomatic phase and relatively low virulence have resulted in a rapid transmission of this virus beyond geographic regions, leading to a pandemic.\(^2\)

The increasing number of confirmed cases and the cardiovascular manifestations induced by the viral infection in addition to the common clinical presentation of respiratory failure caused by COVID-19, has generated considerable concern. Huang et al reported that the 12% of patients with COVID-19 had a concomitant acute myocardial injury, manifested mainly by elevated levels of high-sensitive troponin I. From other recent data, among 138 hospitalized patients with COVID-19, 16.7% had arrhythmias and the 7.2% had acute myocardial injury. However currently there are no specific information to predict if patients with COVID-19 with underlying cardiovascular disease (CVD) will develop myocardial injury during hospitalization.\(^3\)

The activation of macrophages by SARS-CoV-2 leads to the release of metalloproteinases and pro-inflammatory cytokines that increases the procoagulant activity of the vessels and can cause a severe respiratory dysfunction. Patients with severe COVID-19 who needed intensive care unit, usually present systemic inflammation, intravascular coagulopathy with high risk of thrombotic complications, and venous thromboembolism, effects mostly mediated by IL-1.\(^4\)

QTc interval can significantly be prolonged by the systemic inflammatory activation, as commonly observed during acute infection, via direct electrophysiological effects on cardiac repolarization as suggested by emerging data.\(^5\) In fact, many basic experimental studies demonstrated that inflammatory cytokines like tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6) can directly cause the dysfunction of several cardiac ion channels (inflammatory cardiac channelopathies), in particularly K+ channels, leading to ventricular APD prolongation.\(^5\)

Aim of this study is to evaluate the clinical characteristics of dead patients above 50 years of age with mild COVID-19 non-ICU.

**Materials and methods**

**Design of the study**

This is a single center, observational, case series study, conducted enrolling patients admitted from March to April 2020 at the Infectious Diseases Clinic, University “G. D’Annunzio,” SS Annunziata Hospital of Chieti, Italy, with diagnosis of mild COVID-19 pneumonia by real-time PCR on oropharyngeal and nasopharyngeal swabs and >50 years old. Medical records related to the recovery were consulted for each patient, and data regarding anamnesis, laboratory and therapy were collected and tabulated.

We included in this study all patients dead with diagnosis of COVID-19 admitted in our Clinic. Exclusion criteria were: admission to ICU, invasive ventilation use, intubation, and sepsis.

**Data collection**

All the patients admitted had a COVID-19 diagnosis. We collected the demographic data, medical history, underlying comorbidities, clinical symptoms and signs, laboratory findings, chest computed tomography (CT), treatment measures, and outcome data for all hospitalized patients with laboratory confirmed COVID-19.

We collected data about serum creatinine, blood coagulation panel including PT, aPTT ratio, fibrinogen and D-dimer, LDH, CRP, BUN, troponin I, ALT, AST, GGT, ALP, total and fractionated bilirubin, lipase, amylase, and blood glucose levels. To study the heart condition we collected data about electrocardiograms (ECGs) like the heart rate (HR), the PR, QRS complex, and QTc intervals. ECGs were standard 12-lead resting ECGs with computerized ECG interpretation.

Clinicians collected demographic and clinical data about the patients enrolled. Laboratory values and ECG were collected at the time of enrollment and hospitalization (time 0), 7 days after enrollment (time 1) and shortly before death (time 2).

The study protocol was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The patients have signed an information consent for use off-label the drugs.

**Statistical analysis**

Continuous variables were presented as means and standard deviation (SD) or medians and interquartile
ranges (IQR) values as appropriate. Categorical variables were expressed as the counts and percentages in each category. Outcomes of interest were analysed using different linear mixed models. Data have been analyzed using SPSS Advanced Statistical software version 13. In all statistical tests, significance threshold was assumed at \( p \leq 0.05 \).

**Results**

**Characteristics of sample population study**

We documented eight deaths during the period of the study, four of them were male (50%), and all of them were of Caucasian ethnicity with an age of 82 ± 9.7 years. The time of hospitalization before death was 12.5 ± 8.7 days.

All patients had comorbidities: hypertension (7 [87.5%]), diabetes (1 [12.5%]), and heart disease (6 [75%]) were the most common coexisting conditions. Among the cardiac diseases: 7 (87.5%) patients had hypertension, only one patient (12.5%) had heart failure, 3 (37.5%) with atrial fibrillation, 2 (25%) with ischemic heart disease, 4 (50%) with previous stroke. In addition, one patient (12.5%) had dyslipidemia and two of them (25%) had a diagnosis of hypothyroidism.

As far as the cardiological therapy that the patients did before admission: three were on therapy only with diuretics, two patients with beta blockers and three patients were on combination therapy with beta blockers, diuretics, and ACE inhibitors.

Common symptoms included fever [8 (100%)], dry cough (1 [12.5%]), and dyspnea (3 [37.5%]). All patients [8 (100%)] showed local and/or bilateral patchy shadowing on chest computed tomography that is the typical radiological finding in COVID-19. Lymphopenia was observed in 7 patients (87.5%) (Table 1). All patients showed elevated troponin and prolongation of the QTc (\( p < 0.05 \)).

Particularly interesting are the data about troponin levels and QTc prolongation over the observation period. In fact we observed an increase in troponin over time: at T0 the average value of troponin I was 24 pg/mL (IQR, 7.7–40.1), at T1 30.2 pg/mL (14.1–54.4) and T2 56.2 pg/mL (17.1–113.5) with \( p < 0.05 \). Also the parameters of ECG showed elevated heart rate associated with prolongation of the QTc that at T0 had an average value of 438.5 ms (IQR, 414.7–454.2), at T1 448.5 ms (445–498) and at T2 491.5 ms (473–498.7) with \( p < 0.05 \).

| Parameters                  | T0         | T1         | T2         |
|-----------------------------|------------|------------|------------|
| Systolic pressure (mmHg)    | 131.9 ± 20.7 | 120.0 ± 21.0 | 110.0 ± 21.0 |
| Diastolic pressure (mmHg)   | 68.8 ± 8.3  | 70.2 ± 9.5  | 85.2 ± 5.6  |
| Heart rate (bpm)            | 77.4 ± 17.1 | 89.0 ± 18.0 | 89.5 ± 22.3 |
| RBC 10^6 (µ/mmc)            | 4.1 ± 0.7   | 3.8 ± 0.4   | 3.6 ± 0.7   |
| Hb (g/dL)                   | 12.1 ± 1.7  | 11.0 ± 4.0  | 11.2 ± 4.8  |
| Hct (%)                     | 33.0 ± 15.6 | 35.5 ± 0.1  | 32.3 ± 0.1  |
| WBC × 10^3 (µ/µL)           | 8.3 ± 3.7   | 6.9 ± 2.6   | 7.4 ± 2.7   |
| Neutrofili/µL               | 5948.7 ± 3107.4 | 4865 ± 1745.9 | 5450 ± 1716 |
| Linfociti/µL                | 1592.5 ± 514.2 | 1393.7 ± 660.2 | 1251.2 ± 708.8 |
| Monociti/µL                 | 740 ± 675.7 | 665 ± 674.6 | 608.3 ± 493.8 |
| PLT (×10^3/mmcc)            | 218 ± 93    | 223 ± 108   | 258 ± 133   |
| PT (%)                      | 80 ± 38     | 81 ± 25     | 98 ± 44     |
| INR                         | 1.4 ± 0.9   | 2 ± 1.4     | 0.9 ± 0.5   |
| Fibrinogeno (mg/dL)         | 486.5 ± 125 | 520 ± 125   | 528 ± 77    |
| D-dimero (mg/L)             | 1.88 ± 1.25 | 1.7 ± 0.9   | 2.1 ± 1.5   |
| PCR (mg/L)                  | 58.6 ± 67.7 | 112.2 ± 25.1 | 157.2 ± 21.9 |
| PCT (ng/mL)                 | 0.4 ± 0.5   | 0.52 ± 0.2  | 0.7 ± 0.5   |
| LDH (U/L)                   | 222.6 ± 60.2 | 296 ± 219.3 | 312.2 ± 120.2 |
| Creatinina (mg/dL)          | 1.2 ± 1.1   | 0.7 ± 0.4   | 0.6 ± 0.3   |
| AST (U/L)                   | 36.3 ± 25.3 | 39.5 ± 25.3 | 25.6 ± 19.7 |
| ALT (U/L)                   | 22.8 ± 11.3 | 19.5 ± 7.7  | 22.3 ± 22.1 |
| GGT (U/L)                   | 28.25 ± 16.8 | 19.5 ± 11.2 | 36.2 ± 22.3 |
Six (75%) patients received antiviral treatment, including hydroxychloroquine and lopinavir/ritonavir, one patient (12.5%) had also been treated with tocilizumab, a human monoclonal antibody anti IL-6. All patients had anticoagulant therapies, 4 (50%) antiplatelet therapy. Systemic steroid was given to 2 (25%) of cases and to three of them (36.5%) an antibiotic therapy was prescribed (azithromycin, moxifloxacin, and ceftriaxone). All patients received oxygen supplementation at the time of enrollment, five cases received non-invasive mechanical ventilation (62.5%), but at the time of death only three patients (37.5%) had a non-invasive mechanical ventilation, and two patients (25%) had low levels oxygen supplementation.

**Discussion**

This case series study describe the clinical characteristics of dead patients >50 years old with mild COVID-19 non-ICU in a single center in Italy. Dead patients were old and had underlying comorbidities. Some of these patients showed an improvement in pulmonary functions, demonstrated by the reduction in the need of oxygen supplementation. Common symptoms at onset of illness were fever, dry cough, and dyspnea. The typical findings at chest-CT were local and/or bilateral patchy ground glass opacities. The laboratory values showed lymphopenia and elevated levels of C-reactive protein, with normal creatinine, hepatic enzymes. Particularly interesting was an increased troponin level; above the range (>5 pg/mL) in all the patients at the hospital admission, its value has shown an increasing over time, as well as the prolongation of the QTc, until the patients died.

There are two Italian case series on COVID-19; one done on mechanically ventilated patients admitted to the intensive care unit (ICU) that showed how older age and hypertension were associated with the mortality. The other one, a Sardinian study showed that at the univariate analysis, the factors associated with death were older age, hypertension, COPD and £900/mm$^3$ of lymphocytes. The Cox proportional-hazards model a moderate ARDS, and having a number of lymphocyte £900/mm$^3$, were confirmed as statistically significant predictors of death risk.

Evidences from previous studies suggest that older male patients are most susceptible to SARS-CoV-2 infection, as supported by our data. It has been confirmed that increased age was associated with death in COVID-19 patients, and the coexistence of agedness and comorbidity could lead to an even higher risk of death. Older age has been regarded as an important independent predictor of mortality in COVID-19.

Cardiovascular diseases have a high incidence rate in the middle aged and elderly population. Incident cardiovascular complications including new or worsening heart failure, new or worsening arrhythmias, or myocardial infarction are common in patients with pneumonia and are associated with increased short-term mortality. In the present study, eight of eight dead patients had preexisting hypertension and coronary heart disease. Previously, coronary heart disease has also been found to be correlated with acute cardiac events and poor outcomes in influenza and other respiratory viral infections. Logistic regression analysis demonstrated that troponin elevation and prolongation of QTc interval were the independent risk factors for coronary heart disease and heart injury as cause of death in COVID-19 patients.

In this study, dead patients with COVID-19, with severe disease showed abnormalities in some parameters of cardiac markers. As far as we know, this is the first study describing troponin elevation and QTc interval prolongation in COVID-19 hospitalized dead patients. These results suggest a greater chance of cardiovascular and evolution unfortunate complications in patients with these characteristics. The outcome of non-ICU older patients with COVID-19, can be improved with a more careful stratification of the patients and with a frequent monitoring to prevent complications even in patients with an improvement of pulmonary functions.

Angiotensin-converting enzyme 2 (ACE2) acts as a receptor for SARS-CoV-2 entry into cells and contributes to the pathogenesis of COVID-19. Meanwhile, ACE2 is widely expressed in myocytes and vascular endothelial cells. At least, there is theoretically a possibility of direct cardiovascular involvement induced by the virus. The only pathological result of heart biopsy in a fatal case with COVID-19 showed a few interstitial mononuclear inflammatory infiltration, but no other substantial damage in the heart tissue.

The present study has some limitations. First of all only eight patients dead with COVID-19 were included. Secondly, not all laboratory tests were dynamically performed in all patients, including the
counts of lymphocyte subsets and inflammatory cytokines, therefore their role in the pathogenesis of COVID-19 might be underestimated. Last but not least, due to the retrospective study design, echocardiography were not performed in some of the patients.

**Conclusion**

In this observational, retrospective, single-center study, we found that the deaths occurred in the non-ICU population with more than 50 years, also occurred in the presence of improvements of pulmonary function and were all related to troponin elevation and QTc prolongation. Cardiovascular complications, could be predicted with a frequent analysis of troponin levels over time and ECG monitoring. We need more comprehensive and in-depth researches to unveil the cardiovascular involvement in COVID-19 to understand the details of the physiopathology of this emergent disease and for its prevention.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**Ethics approval**

Being a retrospective and observational study, we obtained an acknowledgment from the ethics committee: Comitato Etico delle Province di Chieti e Pescara e dell’Università degli Studi “G. d’Annunzio” di Chieti-Pescara with number ID: rich?g61m, protocol N° 2156.

**Informed consent**

Even if we collected the written informed consent as the patients entered in the Hospital, in accordance to the Committee on Publication Ethics we collected the written informed consent from the patient’s legally authorized representative retrospectively too.

**ORCID iD**

Falasca Katia [https://orcid.org/0000-0002-8795-5410](https://orcid.org/0000-0002-8795-5410)

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