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BCS Editorial

COVID-19: Implications for Cardiologists

Noor Sharrack, MBChB, MRCP, DTM&H

Specialist Registrar in Cardiology
Sheffield Teaching Hospital
Sheffield, United Kingdom

Editor Gershan Davis
Deputy Editor Ahmed Adlan

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Take Home Messages

- Coronavirus disease 2019 (COVID-19) is a rapidly evolving pandemic, which affects patients with a variety of health conditions, including heart disease.
- Patients infected with COVID-19 with pre-existing cardiovascular disease have an increased risk of severe disease and worse outcome, including death.
- Direct cardiovascular effects from COVID-19 include acute myocardial injury, myocarditis, heart failure, arrhythmias and venous thromboembolism.
- Therapies under investigation for treating COVID-19 patients have potential cardiovascular side effects.
- There is no clear evidence to suggest any harmful effect of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in the context of the COVID-19 infection.
- As cardiologists, we need to protect ourselves to ensure we can care for our patients.

Introduction

The novel Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) was declared an official pandemic by the World Health Organization (WHO) on the 11th March 2020.[1]

Patients with COVID-19 and pre-existing cardiovascular diseases have an increased risk of severe disease, characterised by increased need for intensive care support, and death.[2-9] Infection has been associated with multiple direct and indirect cardiovascular complications including acute myocardial injury, myocarditis, heart failure, arrhythmias and venous thromboembolism.[5,6,10] Furthermore, therapies under investigation for treating COVID-19 patients have potential cardiovascular side effects.[6] It is vital therefore that cardiologists have an understanding of the disease and how it affects patients, particularly those with cardiovascular disease who are vulnerable to severe complications and death.

This editorial briefly outlines the background to the COVID-19 pandemic; highlights its clinical presentation; reviews the investigations used to confirm the diagnosis; clarifies the cardiovascular complications and the role of angiotensin converting enzyme-2 (ACE2); and examines the potential therapeutic implications and evolving treatment options. This is a rapidly evolving field and most data is limited to case series and observational data, mainly from China and Italy.

COVID-19 pandemic

SARS-CoV-2 originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, Hubei province, Central China in December 2019.[11] As of the 6th April 2020, according to the WHO there have been 1,214,466 cases of COVID-19 reported worldwide with

About the author

Dr Noor Sharrack is a Specialist Cardiology Registrar in South Yorkshire Deanery. She graduated from the University of Birmingham in 2014 and serves on the Royal College of Physicians Edinburgh trainee and members committee. She plans to specialise in cardiac imaging and undertake research in cardiac magnetic resonance imaging.

67,767 related deaths.[12] As of 6th April 2020, 51,608 people have tested positive for COVID-19 within the United Kingdom (UK) with 5373 related deaths[13] although the actual number of positive cases is expected to be much higher and has been estimated, as of 28th March 2020, to be 2.7% (confidence interval (CI) 1.2-5.4%) of the UK population.[14] Notably the death rate of COVID-19 is much higher compared to seasonal influenza that has a mortality rate of around 0.1%. WHO estimates that around 650,000 people die of influenza related respiratory illness annually worldwide.[15] A recent article, which used WHO data on cumulative number of deaths to March 2020, suggested that mortality rates would be 5.6% (95% CI 5.4-5.8) in China and 15.2% (12.5-17.9) outside of China.[16] While other zoonotic coronaviruses have a higher case fatality rate, Severe Acute Respiratory Syndrome (SARS) 9.6% and Middle East Respiratory Syndrome (MERS-CoV) 34.4%, COVID-19 has already resulted in more deaths than both outbreaks combined.[17] This probably relates to its higher infectivity rate. It is estimated that the R0 value (the basic reproduction number which represents viral infectivity) of COVID-19 is 2.28 to compared to SARS (1.88) and MERS-CoV (0.47).[18]

Clinical presentation and investigations

Just like any other illness, the clinical presentation of COVID-19 is quite variable. The clinical characteristics of mild disease include symptoms common to other viral infections (i.e. fever, cough, myalgia, dyspnoea, diarrhoea and fatigue). A recent study that sampled 1099 laboratory confirmed cases found that the common clinical manifestations included fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%) and headache (13.6%). There were some additional gastrointestinal symptoms observed including diarrhoea (3.8%) and vomiting (5%).[8] **Table 1** indicates common and uncommon symptoms observed in COVID-19. Approximately 1.5 million people used the recent COVID symptom tracker application, developed by researchers from Kings College London of which 26% reported one or more symptoms. Of these, 1702 reported having been tested for COVID-19, with 579 positive and 1,123 negative results. Subsequent analysis has shown that 59% of COVID-19 positive patients reported loss of smell and taste, compared to 18% of those who tested negative for the disease. The reported loss of smell and taste was shown to be a more reliable indicator of infection with COVID-19, compared to fever.[19]

A large study from the Chinese Centre for Disease Control and Prevention indicates that clinical severity of COVID-19 was reported as being mild in 81.4%, severe in 13.9% and critical in 4.7%.[7] Laboratory investigations often show leukopenia and elevated inflammatory markers including CRP. In severe cases, the clinical course can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock and multi-organ failure including acute kidney injury and cardiac injury.[20]

Radiographic features

The most common patterns on chest x-ray are unilateral or bilateral lung infiltrates and computed tomography (CT) of the chest often shows ground glass opacity (56.4%) and bilateral patchy shadowing (51.8%).[18] A study of 1014 patients who received both RT (reverse transcriptase)-PCR and CT in Wuhan found that 97% of cases with RT-PCR confirmed diagnoses had CT findings of pneumonia and concluded that, “CT imaging has high sensitivity for diagnosis of COVID-19”.[9] However CT scans of 112 cases with RT-PCR confirmation from the Diamond Princess Cruise showed that less than two-thirds of cases (61%) had lung opacities on CT and 20% of symptomatic cases had negative CT scans.[21] A recent correspondence article in the Lancet argued that CT does not add diagnostic value and that positive results can only be believed if the pre-test probability of the disease is high. The feeling from authors was that framing CT as pivotal amidst the COVID-19 pandemic could overwhelm resources and was possibly dangerous and could increase the risk of infection to users as CT scanners could become vectors of infection.[22] **Table 1** indicates typical and atypical radiological features observed in COVID-19. **Figure 1** shows an example of the typical evolving CT chest findings in a 77-year old patient infected with COVID-19.

There is evidence to suggest the important role lung ultrasound (US) can play in the diagnosis of COVID-19.[23-25] **Table 1** shows the characteristic ultrasound patterns observed in COVID-19 patients.[26] Lung US has the benefits of being available at the bedside as a portable test; it reduces risk of potential infection to radiology departments and equipment, is reproducible and has no risk of

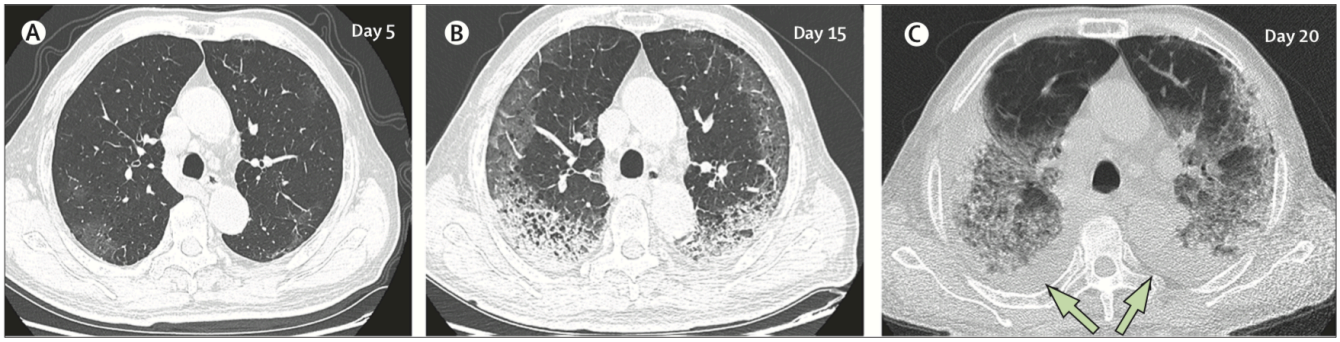

Figure 1. CT chest findings in COVID-19

Transverse thin-section serial CT scans from a 77-year old man (A) Day 5 after symptom onset: patchy ground-glass opacities affecting the bilateral, subpleural lung parenchyma. (B) Day 15: subpleural crescent shaped ground glass opacities in both lungs, as well as posterior reticular opacities and subpleural crescent-shaped consolidations. (C) Day 20: expansion of bilateral pulmonary lesions, with enlargement and denser pulmonary consolidations and bilateral pleural effusions (arrows). The patient died 10 days after the final scan. Adapted from Shi H, Han X, Jiang N et al[28] CT computed tomography.

Table 1. Symptoms, risk factors and tests available for COVID-19

Symptoms	
Common	Fever, Cough, Dyspnea, Anosmia/Dysgeusia, Fatigue, Myalgia, Anorexia, Sputum production, Sore throat
Uncommon	Conjunctivitis, Confusion, Dizziness, Headache, GI symptoms, Haemoptysis, Rhinorrhea, Chest pain
Rare	Cutaneous manifestations
Risk Factors	
	Residence in/travel to location reporting community transmission during the 14 days prior to symptom onset
	Close contact with a confirmed case
	Older age/underlying health conditions
Laboratory Tests	
Viral PCR	Detection of SARS-CoV-2 Viral RNA Routinely collected from nasopharyngeal swab Can also be collected from endotracheal aspirate or bronchiolar lavage (in intubated patients)
Serological Testing	Not available as of yet, but assays in development. Positive for SARS-CoV-2 virus antibodies
Radiological Features	
Chest x-ray	Unilateral or bilateral lung infiltrates.
CT chest	**Typical Features:** Multiple bilateral lobular and subsegmental areas of ground-glass opacity or consolidation[a], crazy-paving pattern, air bronchograms, reverse halo/perilobular pattern. **Atypical features:** interlobular or septal thickening (smooth or irregular), thickening of the adjacent pleura, subpleural involvement, pleural effusion, pericardial effusion, bronchiectasis, cavitation, pneumothorax, lymphadenopathy, round cystic changes.
Lung Ultrasound	B-lines, white lung, pleural line thickening, consolidations with air bronchograms

[a]Usually peripheral or posterior, mainly in the lower lobes, less frequently in right lower lobe. CT computed tomography, PCR polymerase chain reaction, RNA ribose nucleic acid.

radiation. However, it is user dependent and relies heavily on user experience. A recent correspondence published in the Lancet suggested that lung US should replace the stethoscope, reducing the risk of cross infection to medical staff.[27]

Diagnostic criteria

The WHO has updated their definitions of case definitions for suspected cases, probable cases and confirmed cases of COVID-19 (See **Box 1**).[29] **It is vitally important that all doctors ensure they are wearing the right personal protective equipment (PPE) before approaching a suspected or confirmed case of COVID-19.** PPE guidance is changing regularly, so one needs to ensure they are up to date with the latest national and local hospital guidance.[30]

Box 1. WHO diagnostic criteria for COVID-19

Suspected case

A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset.

OR

A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case in the last 14 days prior to symptom onset;

OR

A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g. cough, shortness of breath; AND requiring hospitalisation) AND in the absence of an alternative diagnosis that fully explains the clinical presentation.

Probable case

A suspect case for whom testing for the COVID-19 virus is inconclusive[a].

OR

A suspect case for whom testing could not be performed for any reason.

Confirmed case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

[a] Inconclusive refers to the result of the test reported by the laboratory. WHO World Health Organization.

Comorbidities

Early COVID-19 case reports suggest that patients with certain underlying medical conditions are at a higher risk for complications or mortality.[2-4] A meta-analysis of six studies inclusive of 1527 COVID-19 patients examined the prevalence of cardiovascular disease and reported the prevalence of hypertension, cardiac and cerebrovascular disease, and diabetes to be 17.1%, 16.4% and 9.7% respectively.[2] To date, age>60 years, male sex and presence of comorbidities are known to be the major risk factors for increased mortality in COVID-19. The presence of cardiac injury, myocarditis and ARDS are other strong and independent factors associated with increased mortality risk.[31,32]

Myocardial injury, myocarditis and acute coronary syndromes

COVID-19 has been associated with myocarditis and there have been reported cases of severe myocarditis with reduced left ventricular systolic function.[33,34] Sporadic autopsy cases have shown infiltration of the myocardium by interstitial mononuclear cells.[34] There has also been a report of a 53-year-old lady in Italy with COVID-19 who presented with symptoms typical of myocarditis. This was confirmed on cardiac magnetic resonance imaging showing changes typical of myocarditis.[35] Her coronary angiogram showed no evidence of coronary disease. She was treated with dobutamine, antiviral drugs (lopinavir/ritonavir), steroids, chloroquine and standard medical treatment for heart failure, which resulted in progressive clinical stabilisation. In a case series of 150 patients with COVID-19, there were 68 deaths of which 7% were directly attributed to myocarditis with circulatory failure with a further 33% in which myocarditis was thought to have played a role in their subsequent death.[31]

Myocardial injury, defined by an increase in troponin levels, can occur as a result of supply-demand mismatch (i.e. type 2 myocardial infarction) or non-ischemic myocardial pathologies, such as myocarditis. In COVID-19 a number of patients develop myocardial injury in the context of ARDS and hypoxia and there has been evidence suggesting that troponin levels correlate with disease severity.[2-4,20,31,34] Furthermore, patients with myocardial injury had a higher incidence of ARDS (58.5% vs 14.7%; $p<0.001$) and a higher mortality rate (51.2%

vs 4.5%; p<0.001) than those without cardiac injury. In subsequent analysis, cardiac injury and ARDS were significantly and independently associated with high mortality, with hazard ratios of 4.26 and 7.89, respectively.[36]

Although the incidence of acute coronary syndromes (ACS) in COVID-19 has not been well established, it is likely that the inflammatory processes and hemodynamic changes associated with the illness will confer a higher risk of subsequent plaque rupture in susceptible patients.[6] Additionally, one should remain vigilant to the potential overlapping clinical presentations of ACS and COVID-19.

Cardiac arrhythmia, shock and cardiac arrest

Hypotension, tachycardia, bradycardia, arrhythmia or even sudden cardiac death are common in patients with SARS.[37] Electrocardiographic changes and troponin elevation may signal underlying myocarditis. In a case series of COVID-19 from Wuhan, acute cardiac injury, shock and arrhythmia were present in 7.2%, 8.7% and 16.7% of patients respectively, with preferentially higher prevalence amongst patients requiring intensive care.[5]

Cardiomyopathy and heart failure

Zhou et al reported that 23% of patients with confirmed COVID-19 infection had evidence of heart failure.[4] Patients with heart failure were less likely to survive hospitalisation compared to those that did not (51.9% vs 11.7%).[4] It is worth noting that in this series, it is unclear whether the heart failure observed was an exacerbation of pre-existing left ventricular systolic dysfunction, a new cardiomyopathy secondary to myocarditis or a combination of both factors. In SARS, echocardiography frequently demonstrates sub-clinical left ventricular diastolic impairment, with a higher likelihood of the need for mechanical ventilation in those patients with systolic impairment and reduced ejection fraction.[38]

ACE2 and potential therapeutic implications

Studies have demonstrated that SARS-CoV2 as well as other coronaviruses use the ACE2 protein for cell entry. ACE2 is a type 1 integral membrane protein that is highly expressed in lung alveolar cells providing the main entry site for the virus into human hosts. ACE2 also serves a role in lung protection and therefore viral binding to this receptor deregulates a lung protective pathway, contributing to viral pathogenicity.[6] The complications stemming from modulation of this receptor are not fully understood and are due to be tested in upcoming clinical trials. Despite some literature suggesting the possible harmful effects of ACE inhibitors and angiotensin receptor blockers (ARB) in the setting of COVID-19, The American College of Cardiology, American Heart Association, British Cardiovascular Society, the British Society for Heart Failure and the Council on Hypertension of the European Society of Cardiology all recommend that patients should continue their ACE and ARB inhibitors unless directly advised to stop by a medical practitioner.[39-41] Subsequently, an article has been recently published in the New England Journal of Medicine suggesting that abrupt withdrawal of RAAS (Renin-Angiotensin-Aldosterone-System) inhibitors in high-risk patients, including those with heart failure, or previous myocardial infarction, may result in clinical instability and adverse health outcomes. The authors confirm that insufficient data is available to determine the effects of RAAS inhibitors in COVID-19, and proposed an alternative hypothesis suggesting that ACE may be beneficial rather than harmful in patients with lung injury.[42]

Antiviral therapies and other treatment options

The mainstay of treatment remains supportive care and treatment of complications. To date, no approved preventative vaccines or approved therapies are available for COVID-19, although several are being actively studied. Remdesivir is currently being trialled in moderate and moderate to severe COVID-19 infection. Chloroquine, used primarily as an antimalarial agent, has also been demonstrated to have an inhibitory activity in SARS-CoV2 in vitro.[43] In addition, a number of immune modulating drugs are being investigated. These drugs all have potential cardiac side effects namely cardiac toxicity and QT prolonging effects with chloroquine. The US Food and Drug Administration have approved the use of plasma from recovered patients to treat patients with COVID-19 who are critically ill.[44]

Conclusion

COVID-19 is a rapidly evolving pandemic with significant unknowns. It is clear that patients with underlying cardiovascular conditions have a higher risk of severe infection and death. This infection causes both direct and indirect cardiovascular effects as described in the literature but there may be additional longer-term sequelae, which have not yet been identified. Cardiologists must do their best to protect vulnerable patients as well as themselves in order for them to be able to provide care to the patients that need them during this difficult time.

Disclosures

None.

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