Chapter

Coronavirus Disease: Epidemiology, Aetiology, Pathophysiology and Involvement of the Cardiovascular System

David C. Gaze

Abstract

Since the emergence in China of coronavirus disease (COVID-19) in December 2019; the virus causing the pandemic has infected the human population in almost every country and territory on the globe. At the time of writing there are over 84 million confirmed cases of infection and over 1.8 million deaths globally. Rates of infection differ as does the number of severe cases and subsequent deaths between countries and continents. This is due in part to lockdown measures, social distancing and wearing of face coverings. It is also reflected by how healthcare systems record coronavirus deaths along with access to testing as well as tracking and tracing of infected individuals. Symptoms of COVID-19 include a novel persistent cough, fever and anosmia (loss of smell). In most cases, such symptoms are mild. A small proportion of those who become infected however, have a severe reaction to the disease affecting multiple organ systems and often require respiratory support in the intensive care setting. One such physiological system affected is the cardiovascular system. This is likely due to the increased number of ACE2 receptors in co-morbid cardiac pathologies. ACE2 receptors serve as the entry port for the coronavirus into human cells. Those individuals with underlying cardiovascular risk factors are therefore disproportionately at risk of COVID-19 infection. This chapter reviews the aetiology and epidemiology of the coronavirus infection; potential pathophysiological mechanisms of disease involving the cardiovascular system including the clinical utility of biomarkers, electrocardiography and echocardiography as well as autopsy cardiac pathology and histopathology.

Keywords: coronavirus disease, cardiovascular system, ACE2 receptors, pathophysiological mechanisms

1. Introduction

Coronavirus disease (COVID-19) is an emerging viral disease affecting humans. In December 2019, a small series of cases of a pneumonia-like illness presented to a hospital in Wuhan, Hubei province in China. The patients displayed bilateral pulmonary infiltrative lesions on chest x-ray. The disease was initially named 'viral pneumonia of unknown cause'. Many of those presenting with similar symptoms had visited or been closely associated with a local wholesale seafood market which also sold

exotic species such as civets, snakes, rats and bats. The Chinese Centre for Disease Control and Prevention (China CDC) identified the virus as a novel coronavirus (nCoV) on 7th January 2020 and renamed the disease 'pneumonia caused by a novel coronavirus. Subsequently on 30th January 2020, the World Health Organisation (WHO) referred to the disease as 2019-nCoV. The *Coronaviridae* study group of the International Committee on Taxonomy of Viruses (ICTV) officially named the virus Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) on 11th February 2020. The WHO also announced a name change to *CO*rona*VI*rus *D*isease 2019 (COVID-19). The change reflected the greater reporting of a wide range of clinical presentations and multiple organ system involvement in severe cases of the disease. At the same time, it became apparent the disease was spreading significantly in Hubei Province due to an increase in numbers of cases with no identifiable association to the seafood market, demonstrating community (person-to-person) transmission.

The rate of escalation of COVID-19 infection is alarming. This is detailed in the following statistics (provided by many resources online via China CDC, news outlets and social media coverage). A retrospective epidemiological analysis by China CDC indicated there were 104 symptomatic cases by 31st December 2019. All cases were contained in Hubei province. Between 1st and 10th January 2020, this had risen to 566 cases showing symptoms in Hubei, with a further 87 cases in 19 other provinces. On January 20th 2020, 5 cases were reported in Beijing and 2 in Shanghai. Further analysis demonstrates that the number of cases of COVID-19 present in

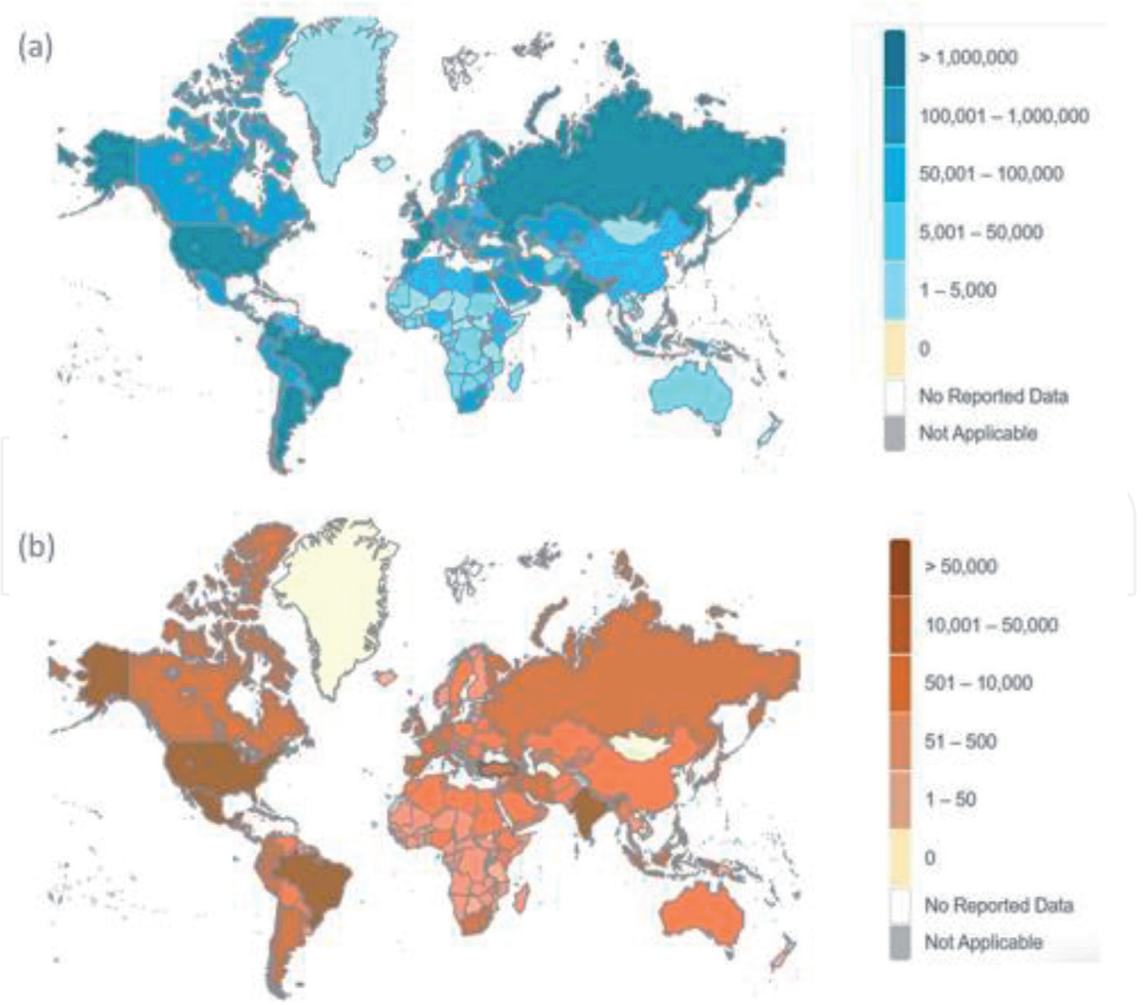

Figure 1.
Global epidemiology of COVID-19. (a) Confirmed cases of coronavirus and (b) deaths from coronavirus. (source WHO live situation dashboard www.covid19.who.int).

China by 31st January 2020 reached as staggering 32,642. 75% of these were in Hubei province. The incidence of the disease in mainland China had escalated to over 74,000 cases by 19th February 2020 along with 65 cases and 5 deaths in Hong Kong, 10 confirmed cases in Macao and 24 cases and one death in Taiwan.

From mid to late January countries other than China began reporting COVID-19 cases. The first non-mainland case was a Chinese national from Wuhan who travelled to Thailand and tested positive for COVID-19 on the 13th January 2020. The first reported case outside of Asia was announced on the 21st January 2020 in the United States of America (USA). At the end of February, the WHO declared the epidemic as a 'Public Health Emergency of International Concern' with evidence of infected cases in South Korea (2,337), Japan (210), Italy (650), Iran (245), Singapore (96) and USA (59). The cases in Japan are of note as they are associated with a contained infection on the Diamond Princess cruise ship. The ship departed Japan on 20th January 2020. Five days later a passenger developed a fever and tested positive on 1st February 2020 in Hong Kong. The ship returned to Japan and was placed in quarantine. By 12th February 492 passengers were tested of which 174 were positive for COVID-19. By 19th February 2020, the number of passengers infected rose to 621 and 705 nine days later. On 11th March 2020, at the daily briefing by the director general, Dr. Tedros Adhanom Ghebreyesus, the WHO declared COVID-19 as an offically recognised pandemic [1].

It is now a year since the initial outbreak in China. In this short time the WHO report via their live situation dashboard [2] to date (5th January 2021) 84,233,579 confirmed cases globally of which 1,843,293 individuals have died (**Figure 1**). What is shocking and apparent is the upward escalation of these figures on a daily basis, especially in the winter months in the Northern Hemisphere.

2. Novel SARS-CoV-2 variants

Late in 2020, two variants of the SARS-CoV-2 virus have been identified. The first was identified in September and sequenced in the United Kingdom [3]. The 'UK Kent variant' as it is commonly known has spread rapidly both in the UK and internationally. Since 26th December 2020, cases of the new UK Kent Variant have also been reported in other EU/EEA countries (Belgium, Denmark, Finland, France, Germany, Iceland, Ireland, Italy, the Netherlands, Norway, Portugal, Spain and Sweden) and globally (Australia, Canada, Hong Kong SAR, India, Israel, Japan, Jordan, Lebanon, South Korea, Switzerland, Singapore). The second variant originated in South Africa and is due to the mutation E484K; known as 501.V2. This variant was first detected in October 2020 and is associated with over 300 cases as of 26th December 2020. Both variants are highly transmissible, but data suggest they do not increase the severity of COVID-19 infection [4].

The first variant was identified following a surge in positive cases in the County of Kent in South East England and has spread extensively into London and beyond (**Figure 2**). The variant was named as variant under investigation (VUI) followed by year, month and number; thus, the designation given was VUI-202012/01 which was changed to variant of concern (VOC-202012/01). The variant is defined by 23 novel mutations. 13 of which are non-synonymous, 4 deletion and 6 synonymous. Of concern is nucleotide A23063T in the spike protein representing mutation N501Y. This mutation is located in the receptor-binding domain and is associated with increased binding affinity to ACE2; making viral entry into host cells easier than with the original strain, thus increasing transmissibility. Although more transmissible, recent data suggest this variant is less likely to cause severe infection and is likely to respond to the current vaccination programme [5].

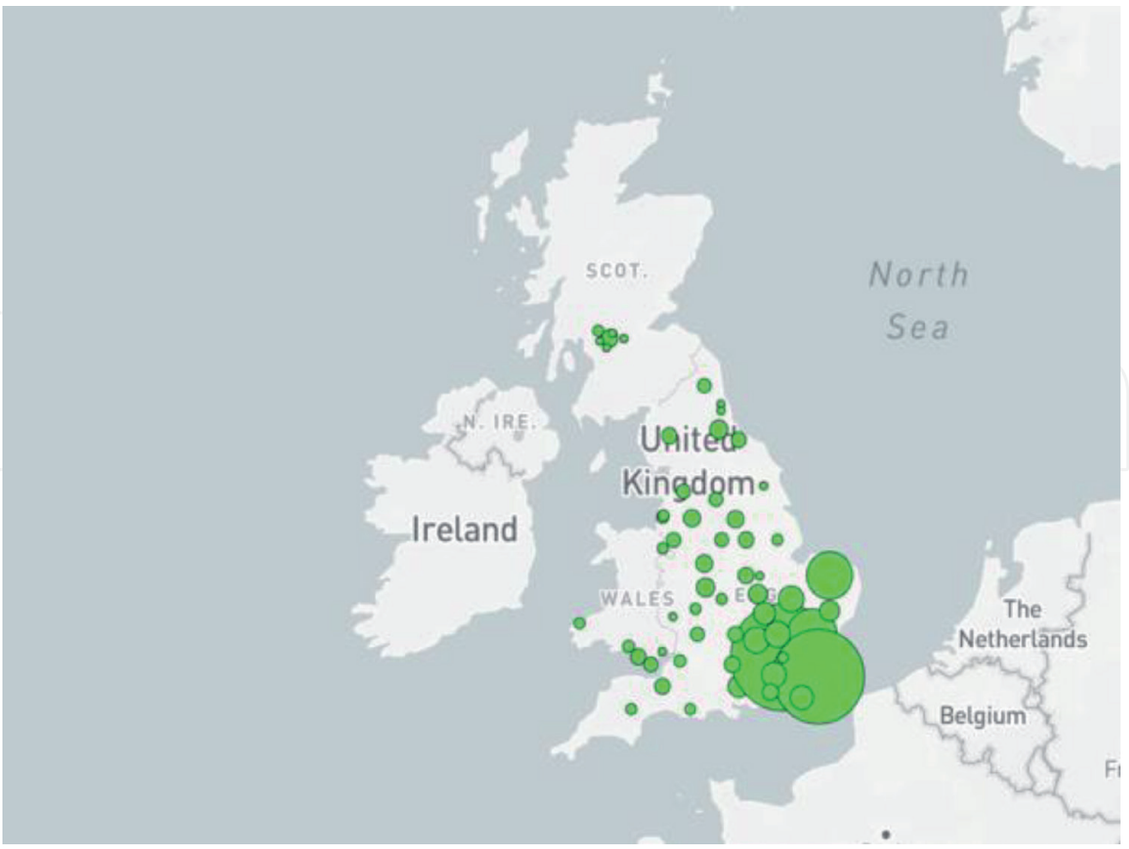

Figure 2.
Distribution of confirmed sequenced cases of VOC202012/01 as of 6th January 2021. [source: https://beta.microreact.org/project/vVnFfZG703qYUJ6bnDs3Jo-cog-uk-2020-12-20-sars-cov-2-in-the-uk].

3. Coronaviruses

3.1 Taxonomy and morphology

Coronaviruses are a large family of viruses found in animals such as camels, dogs, rats, cattle, mice, rats and bats; as well as several viruses known to infect humans. They were first discovered in 1968 and named *Coronaviridae* in 1975 by the ITCV. The viruses are positive-sense single stranded RNA viruses with 26 to 32 kb genomes and are classified into *Alpha, Beta, Gamma* and *Delta* genera (**Figure 3**). The viruses that infect mammals are *Alpha* and *Betacoronaviruses*. In humans, pathogenic coronaviruses include SARS-CoV, SARS-CoV-2, MERS-CoV, HCoV-HKU1, HCoV-229E, HCoV-NL63 HCoV-OC43. Most are inconspicuous and develop into common colds and mild-flu like symptoms, but recently since the emergence of SARS and MERS and now SARS-CoV-2, an increasing number of severe illnesses are developing associated with novel coronaviruses in humans.

Morphologically, the viral particle of coronaviruses are encased in a bilipid layer with three glycoproteins on the surface designated as membrane (M protein), envelope (E protein) and spike (S protein) proteins (**Figure 4a**). These give the virus the characteristic protrusions on the surface akin to a medieval European crown or *'corona'* hence the name coronavirus. An electron micrograph of viral particles isolated in alveolar tissue from the first infected case in the United States is shown in **Figure 4b**.

Utilising cryptoelecton tomography (Cryo-ET), Yao and colleagues determined the detailed molecular structure of the novel SARS-CoV-2 enveloped virus and elucidated the mechanism of packing the ~30 kb long single RNA into the 80 nm diameter luminal space [7].

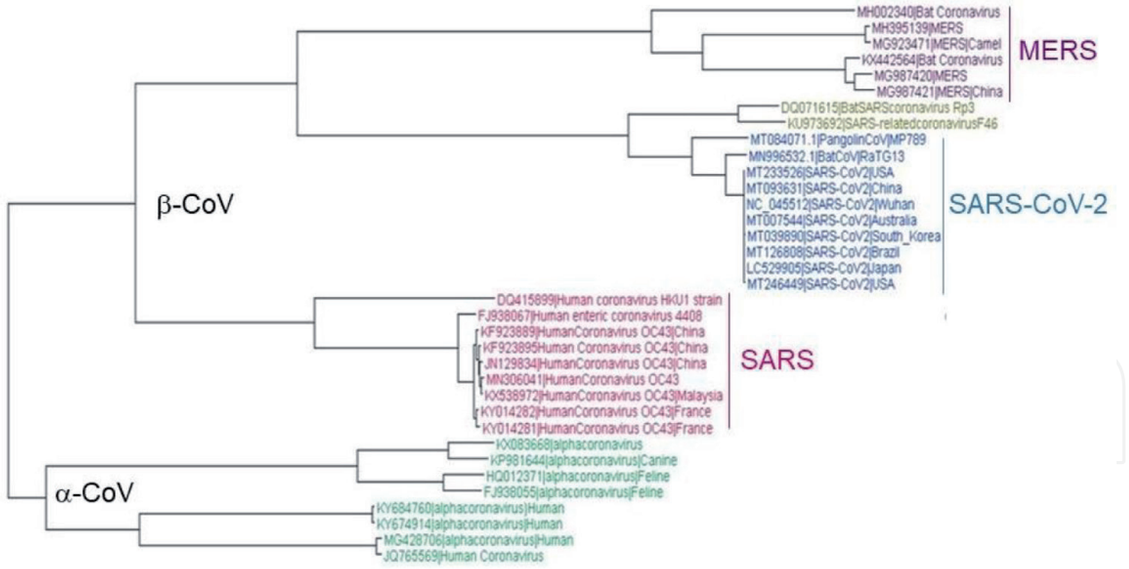

Figure 3.
Phylogenic tree of alpha and beta coronaviruses. MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; SARS-COV-2, severe acute respiratory syndrome coronavirus 2.

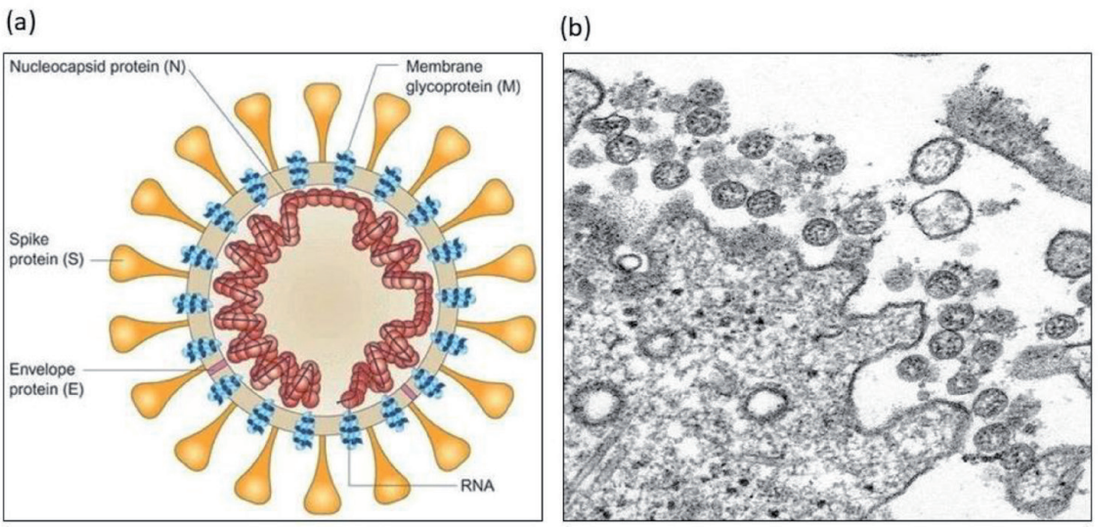

Figure 4.
(a) Schematic structure of a coronavirus particle [source: Peiris et al., [6]] (b) transmission electron microscopy image of an isolate from the first case of COVID-19 in the USA. The spherical extracellular viral particles contain cross-sections through the viral genome seen as black dots [source: cdc.gov].

3.2 Cellular entry of SARS-CoV-2

The SARS-CoV-2 virus enters human cells via interaction of the spike protein with the Angiotensin Converting Enzyme 2 protein (ACE2) [8]. ACE2 is integral to the renin-angiotensin-aldosterone (RAAS) system. Originally thought to have a systemic effect on maintenance of blood pressure and electrolyte balance, it has been found to be involved in inflammatory responses in many tissues including the cardiovascular system [9]. Activation of the RASS system has been associated with the development of hypertension, myocardial infarction, chronic heart failure, diabetes and inflammatory processes in lung tissue [10]. SARS-CoV-2 and ACE2 protein interaction is like the SARS-CoV virus responsible for the original SARS outbreak [11].

ACE2 is a metallopeptidase and is found in virtually all cell types. It is highly expressed on cell surfaces in lung alveolar epithelium, intestinal enterocytes as well

as on vascular endothelial cells [12]. This is especially important in those individuals with underlying cardiovascular diseases as expression of ACE2 in the vasculature is altered [13]. This will be detailed further in the chapter under cardiovascular involvement. Following internalisation via vesicle entry, the ACE2 surface proteins are downregulated, potentiating the increasing physiological effects of angiotensin II (**Figure 5**) via proinflammatory mediators [14].

3.3 Routes of transmission of SARS-CoV-2

The major route of transmission in the human population is from person-to-person via respiratory droplets when infected individuals cough, sneeze and talk when in close contact with another person [15]. Susceptible individuals inhale droplets shed from an infected individual near one another. The risk of infection depends on the size of the particles and droplets, the extent of viral shedding from the infected individual, the force of expulsion of droplets from an infected individual, the proximity between infected and uninfected individuals as well as environmental factors such as air density, humidity and wind speed [16]. Aerosol transmission is an alternative route of infectivity; however, this has been subject to significant debate and scientific study.

Aerosol transmission occurs when proteins and pathogens float in the form of aerosols after droplets dry out. This may be possible with SARS-CoV-2 in enclosed areas if individuals are exposed to high levels of infected aerosol material such as in care home settings and hospital wards; thus, pose a risk to healthcare workers and others in close contact with infected individuals over a long period of time. Aerosol transmission is often successful with particles with a diameter of 5–10 μm and can be carried over a large distance, whereas droplets are often larger than 10 μm and fall from the air within 1 metre hence the global adoption of spacing between individuals of 1–2 metres [17].

Oral-faecal transmission is another potential route of person-to-person transmission [18]. SARS-CoV-2 has been detected in faecal material from known COVID-19 patients [15, 19]. This is unsurprising given the clinical gastrointestinal manifestations in some individuals. This poses as a rapid transmission route in

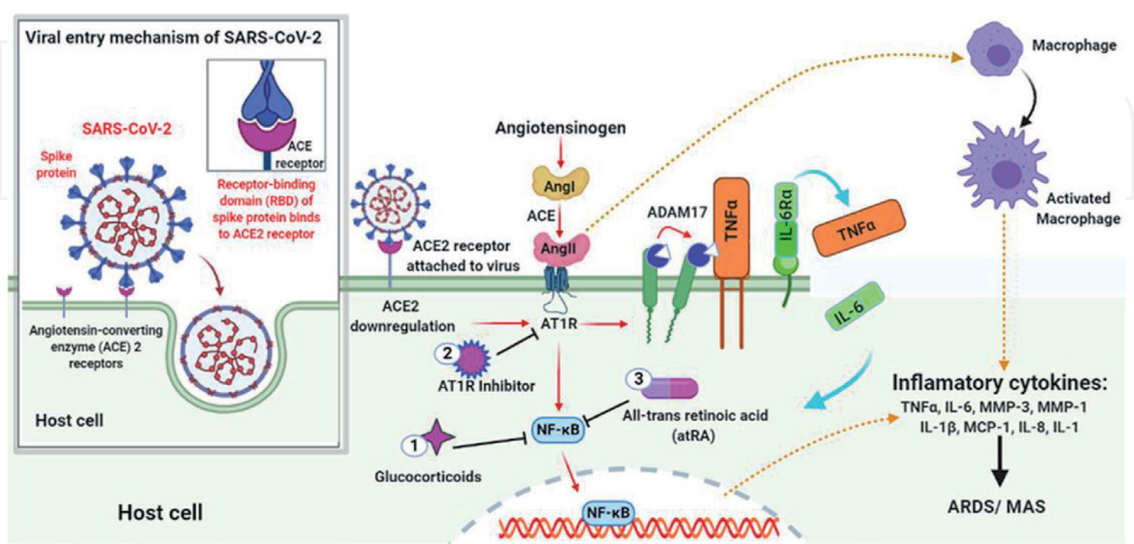

Figure 5.
Viral entry of SARS-CoV-2 in host cells via the ACE2 surface protein. Following entry ACE2 is downregulated resulting in upregulation of angiotensin II (Ang II) which via its AT1R receptor induces NF-kB signalling pathways to increase expression of inflammatory cytokines such as interleukins (IL-1, IL1β, IL-6), matrixmtalloproteinases (MMP-1, MMP-3) and tumour necrosis factor alpha (TNF-α). [source: Banu et al. [14]].

persons unable to maintain good hygiene such as neonates/infants, the infirm and the elderly with cognitive decline such as dementia. It is also a source of environmental viral transmission in developing countries with poor sanitation and no running clean water and soap for adequate hand washing. This has wider impact on those healthcare systems who provide screening of faecal material for colorectal cancer screening [20].

SARS-CoV-2 has not been detected in semen from individuals who have either recovered from or have active COVID-19 infections [21, 22], suggesting sexual transmission is very unlikely. Maternal-fetal transmission however has been described in a small number of clinical cases. A neonate born in Wuhan to a COVID-19 positive woman tested positive for COVID-19 in a nasopharyngeal swab taken 2 days after birth, however this does not confirm maternal-fetal transmission. Oher studies refute vertical intrauterine transmission from mother to child [23, 24] however a recent meta-analysis suggests vertical transmission is possible normally in the third trimester but the incidence is low at 2–3% [25]. This is in part due to the ACE2 receptor portal of SARS-CoV-2 entry into cells being expressed in low concentrations at the maternal-fetal barrier, limiting the route of vertical transmission.

4. General clinical presentation of COVID-19

With the emergence of the pandemic in earnest at the beginning of 2020, the medical and scientific literature has been flooded with case reports and small clinical series often on a regional (district/country) basis. In general, the clinical presentation of patients with SARS-CoV-2 is very similar to that of other coronavirus infections in humans. For the majority of those infected, individuals are either asymptomatic or have a mild fever, novel dry cough or anosmia (loss of smell).

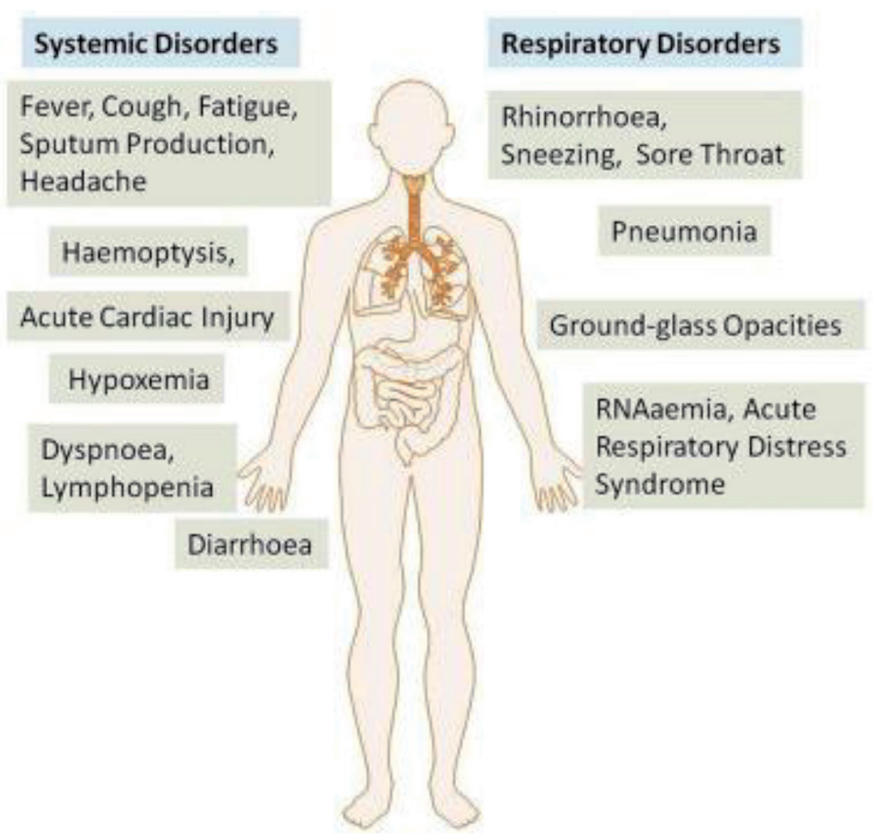

Figure 6.
Respiratory and systemic signs and symptoms associated with COVID-19 [source: Rothan and Byareddy [26]].

	Participants (n)	Value (%)	95% CI
Clinical Presentation			
Fever	15,921	78.8	76.2 to 81.3
Fatigue	13,680	32.2	28.0 to 36.6
Myalgia	10,728	21.3	18.1 to 24.9
Malaise	2,526	37.9	29.5 to 47.1
Respiratory symptoms			
Cough	12,782	53.9	50.0 to 57.7
Expectoration	6,072	7.5	5.7 to 9.6
Chest pain	3,512	9.0	6.2 to 13.1
Shortness of breath	11,205	18.9	15.7 to 22.8
Gastrointestinal symptoms			
Nausea	5,599	6.9	5.3 to 9.1
Vomiting	7,484	4.7	3.8 to 5.8
Diarrhoea	12,142	9.5	7.8 to 11.5
Prognosis			
Renal injury	77,679	3.6	1.2 to 10.1
Hepatic injury	77,331	7.9	2.6 to 21.7
Cardiac Injury	1,417	9.4	4.5 to 18.8
Mechanical ventilation	6,152	7.1	4.5 to 11.0
Mortality	52,808	5.6	4.2 to 7.5

Table 1.
Clinical characteristics and outcomes in COVID-19. Analysis of 281,461 confirmed cases. 95% CI, confidence interval. [source, data from Li et al. [27]].

In the small minority of those who are severely affected, the overriding clinical presentation is of respiratory distress however other symptoms are case-dependent.

The reported clinical characteristics and prognosis of COVID-19 patients varies greatly (**Figure 6**). A recent comprehensive meta-analysis has been performed of clinical characteristics, risk factors and outcomes by Li and colleagues [27]. This vast analysis includes 212 studies from 11 countries involving 281,461 laboratory confirmed COVID-19 cases. The mean age of patients was 46.7y (95%CI 42.8y to 50.6y) with 51.9 (95%CI 50.4 to 53.2) males. The mean time of illness onset to hospital admission was 5.5 days (95%CI 4.6 to 6.4 days) with an incubation period of 5.3 days (95%CI 4.5 to 5.9 days). Clinical presentation characteristics and outcome are summarised in **Table 1**. 79% of subjects were febrile and 53% developed a cough. Renal and hepatic injury occurred in 4% and 7% respectively but cardiac injury was higher at 9%. Overall mortality was reported to be 6% but this differed greatly by country. Mortality was significantly associated with age, male sex, the presence of hypertension or diabetes mellitus [27].

5. Chest imaging

Thoracic imaging is an important diagnostic tool in screening, early diagnosis and monitoring of patients with COVID-19. Although computed tomography (CT) is the gold standard, chest x-ray (CXR) is a cheap, readily available and a

faster alternative. CXR lacks sensitivity for diagnosis in the early presentation of COVID-19 being 55% within two days, increasing to 79% at 11 days from onset of symptoms. Specificity decreased over time from 83–70% at ≤2d and > 11d respectively [28]. In approximately 60% of cases, CXR reveals interstitial and airspace opacities in an IA pattern. This increased over time from 51% at ≤2d vs. 73% at >11d [28]. Normal and mild severity CXR findings were the largest factor behind false-negative CXR and often associated with young age and some ethnic groups. In a real-world reader performance study by Cozzi and colleagues [29], experienced radiologist (>10 y experience) reported CXR with higher specificity than less experienced (<10 y experience) radiologists. Comparative CXR images from different respiratory diseases and a normal CXR are shown in **Figure 7**.

Computed tomography (CT) is the preferred radiological procedure for diagnosis. A Cochrane review of CT for diagnosis of COVID-19 found that in 84 studies with 8,279 participants; the pooled sensitivity for diagnosis was 86% (95%CI 90–95%) with a very low specificity of 18% (95%CI 4–56%) [31]. A retrospective study of chest CT findings in 121 symptomatic patients in 4 centres in China has been reported [32]. The classical findings were bilateral and peripheral ground-glass

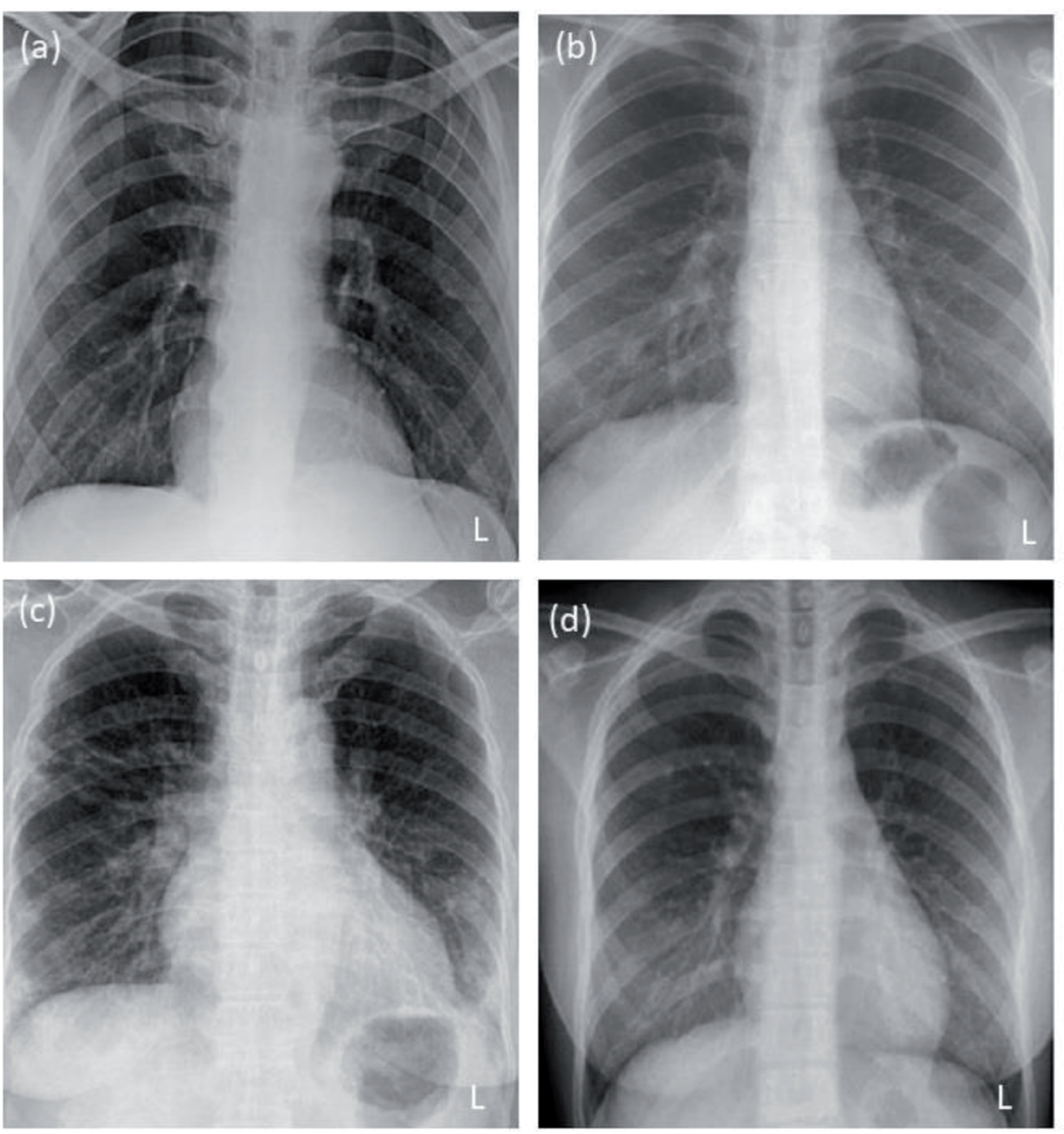

Figure 7.
Comparative chest X-ray findings in (a) normal CXR (b) SARS (c) MERS (d) COVID-19. [source: Images adapted from Pereira et al. [30]].

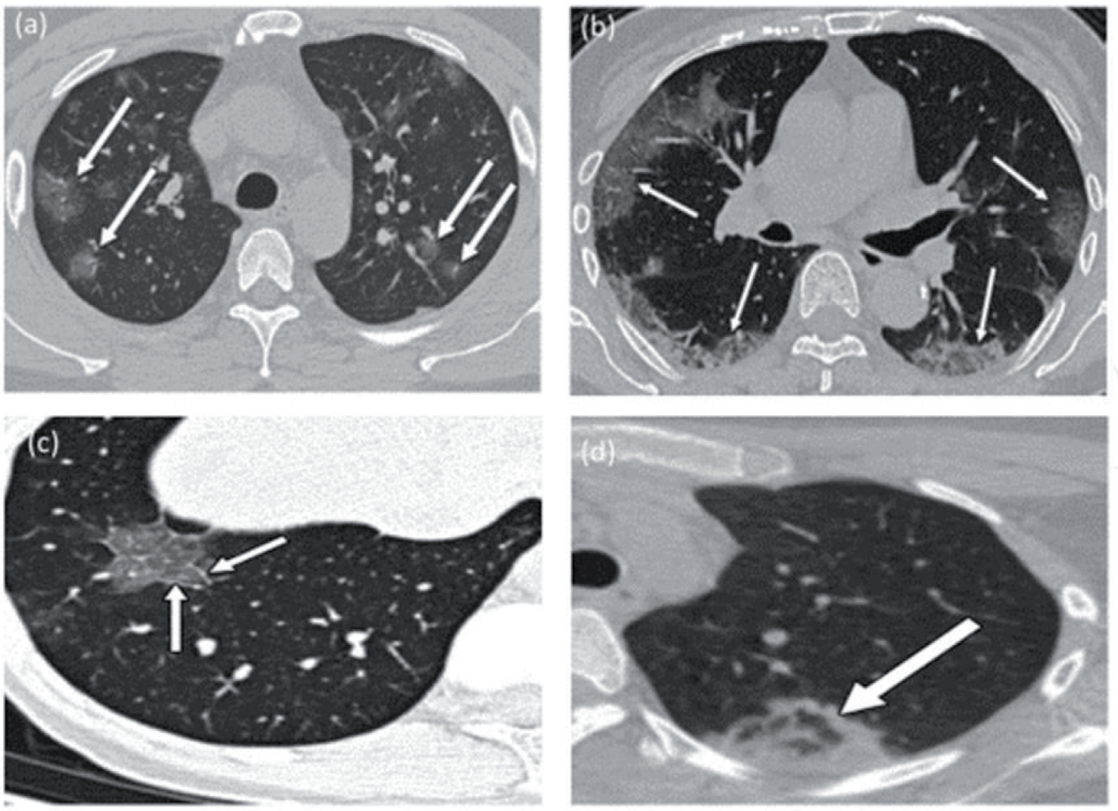

Figure 8.
Representative characteristic findings of COVID-19 infection on thoracic CT imaging: (a) axial CT image obtained without intravenous contrast. 36y male showing bilateral ground-glass opacities in upper lobes with rounded morphologies (arrows); (b) axial CT image. 65 y female, showing bilateral ground-glass and consolidative opacities with striking peripheral distribution (arrows); (c) axial CT image obtained without intravenous contrast material in a 43 y female, demonstrating crazy-paving pattern manifested by right lower lobe ground-glass opacification with interlobular septal thickening (arrows) with intralobular lines. (d) Axial CT image obtained in a 22y female, showing an area of faint ground-glass opacification in left upper lobe with a ring of denser consolidation or reverse halo sign (arrow). [source: Images modified from Bernheim et al. [32]].

consolidative opacity. 56% of subjects had normal CT images in the early phase (0 to 2 days) of the disease but more frequent in longer infections with consolidation, bilateral and peripheral and greater total lung involvement. Bilateral involvement occurred in 28%, 76% and 88% of early (0–2 days), intermediate (3–5 days) and late (6–12 days) infection times respectively. Further notable CT findings include linear opacity, crazy-paving patterns and reverse halo sign (**Figure 8**).

Following isolation and treatment, most COVID-19 patients stabilise and become well. Further CT imaging demonstrates regression of infection with absorbed lesions, and some cord-like shadows.

6. Gastrointestinal symptoms in COVID-19

Gastrointestinal (GI) symptoms are emerging in patients with COVID-19. This is due to the presence of the ACE2 receptor expressed in the GI tract [33, 34].

COVID-19 patients present with GI symptoms such as diarrhoea (10% of patients) with nausea and vomiting less common [35]. In a meta-analysis of 35 studies, 29 studies reported gastrointestinal symptoms in 6,064 COVID-19 patients with a pooled prevalence of gastrointestinal comorbidities of 4%. (95% CI 2 to 5%; range 0 to 15%; I^2 = 74%). The pooled prevalence of digestive symptoms was 15% (10 to 21%; range: 2 to 57%; I^2 = 96%) with nausea or vomiting, diarrhoea, and loss of appetite being the three most common [36].

7. Cardiovascular findings in COVID-19

In addition to respiratory and gastrointestinal symptoms, cardiovascular involvement is also common amongst patients with COVID-19. The symptoms are wide-ranging in manifestation and severity and are more common in the elderly and those hospitalised with the infection. Previous influenza epidemics have been associated with an increased prevalence of myocardial infarction, myocarditis and chronic/congestive heart failure [37]. Both SARS and MERS were associated with either bradycardia, tachycardia, cardiomegaly, diastolic impairments, cardiac arrest, cardiomegaly and acute cardiac failure [38–40].

Patients with cardiovascular risk factors or established cardiovascular disease disproportionately suffer with severe forms of the infection with worse clinical prognosis and outcome. In one of the earliest reports of clinical characteristics of COVID-19 from Wuhan China; 14% of 138 patients demonstrated baseline cardiovascular disease and 31% had hypertension [41]. Similar data has been reported in other population studies from Wuhan, China [42–44]; Italy [45, 46]; Iran [47], United Kingdom [48] and the USA [49] to varying cardiac involvement.

The pathophysiological mechanism of cardiac injury in COVID-19 infection are similar to those associated with other influenza pandemics and human coronavirus diseases (SARS and MERS). Although the pathophysiological mechanisms injury is not fully established in COVID-19 patients, it is likely that the elevation is related to (1) Systemic inflammatory involvement, cytokine storm mediated through T-cell and monocytes resulting in myocarditis. Often patients have concomitant elevations in C-reactive protein (CRP), eosinophil sedimentation rate (ESR) (2) Hypercoagulability.

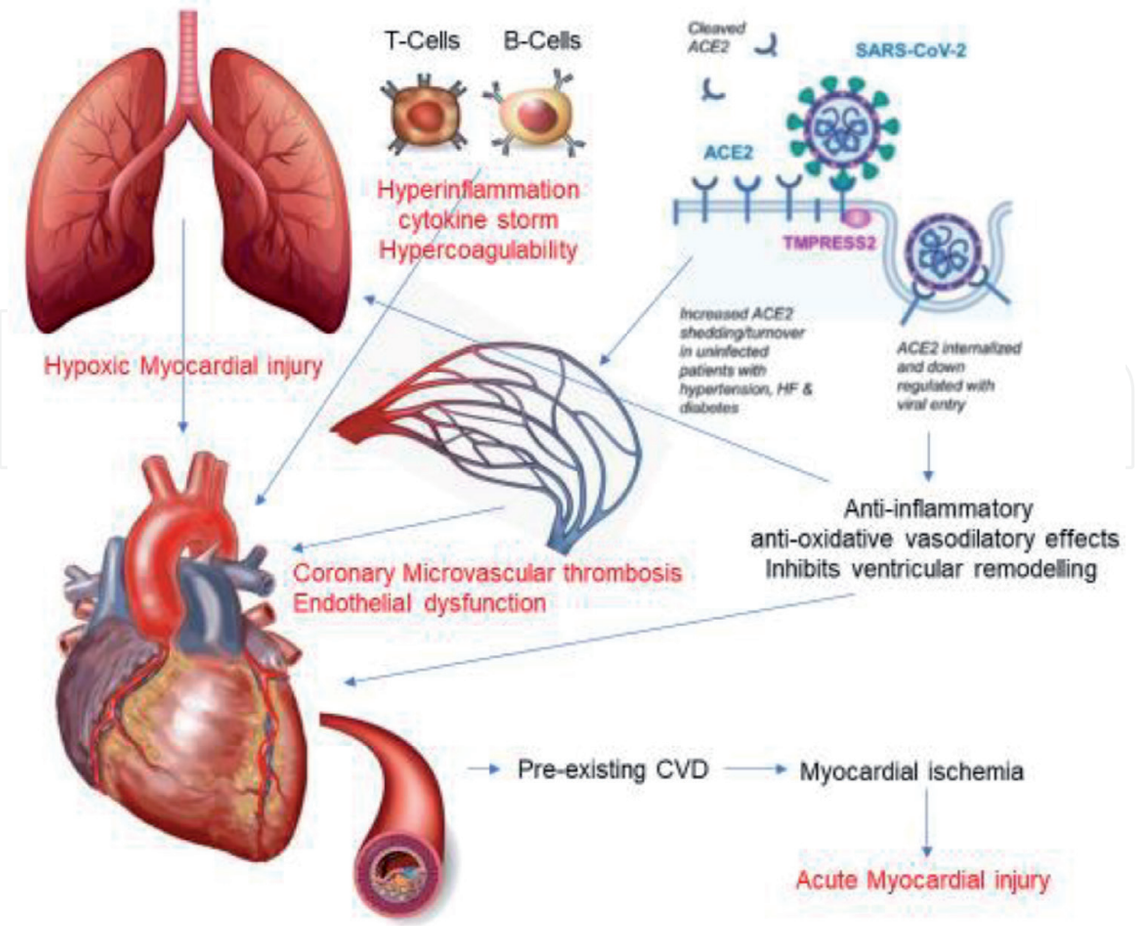

Figure 9.
Pathophysiological mechanisms of acute myocardial injury in COVID-19 infection.

Haematological differentials along with abnormal clotting factors and elevated D-dimer result in haemostasis and thrombosis as evident of coronary microvascular disease. (3) Endothelial injury causing diffuse disruption to the vasculature in several organs including the heart. (4) Down regulation of ACE2 expression in cardiomyocytes and loss of the protective signalling pathway (5) Inflammatory and stress response causing plaque rupture in those subjects with active coronary artery disease (**Figure 9**).

8. Biomarker evidence of myocardial injury in COVID-19

A significant proportion of patients requiring hospitalisation, intensive therapy and the need for mechanical ventilation demonstrate elevation of biomarkers of cardiac injury [42–44, 50–55], namely cardiac troponin T (cTnT); cardiac troponin I (cTnI) and the natriuretic peptides N-terminal pro-B-type natriuretic peptide (NTproBNP) and the active hormone b-type natriuretic peptide (BNP).

The evidence of cardiac injury in COVID-19 is wide ranging and its association with mortality differs between studies. Li and collages performed a meta-analysis of 28 studies involving 4,189 individuals with COVID-19. Elevated cardiac biomarkers (cTn, creatine kinase-MB, myoglobin and NTproBNP were associated with the severe forms of infection compared to subjects with mild forms of the disease (**Figure 10**). In addition, those with evidence of COVID-19

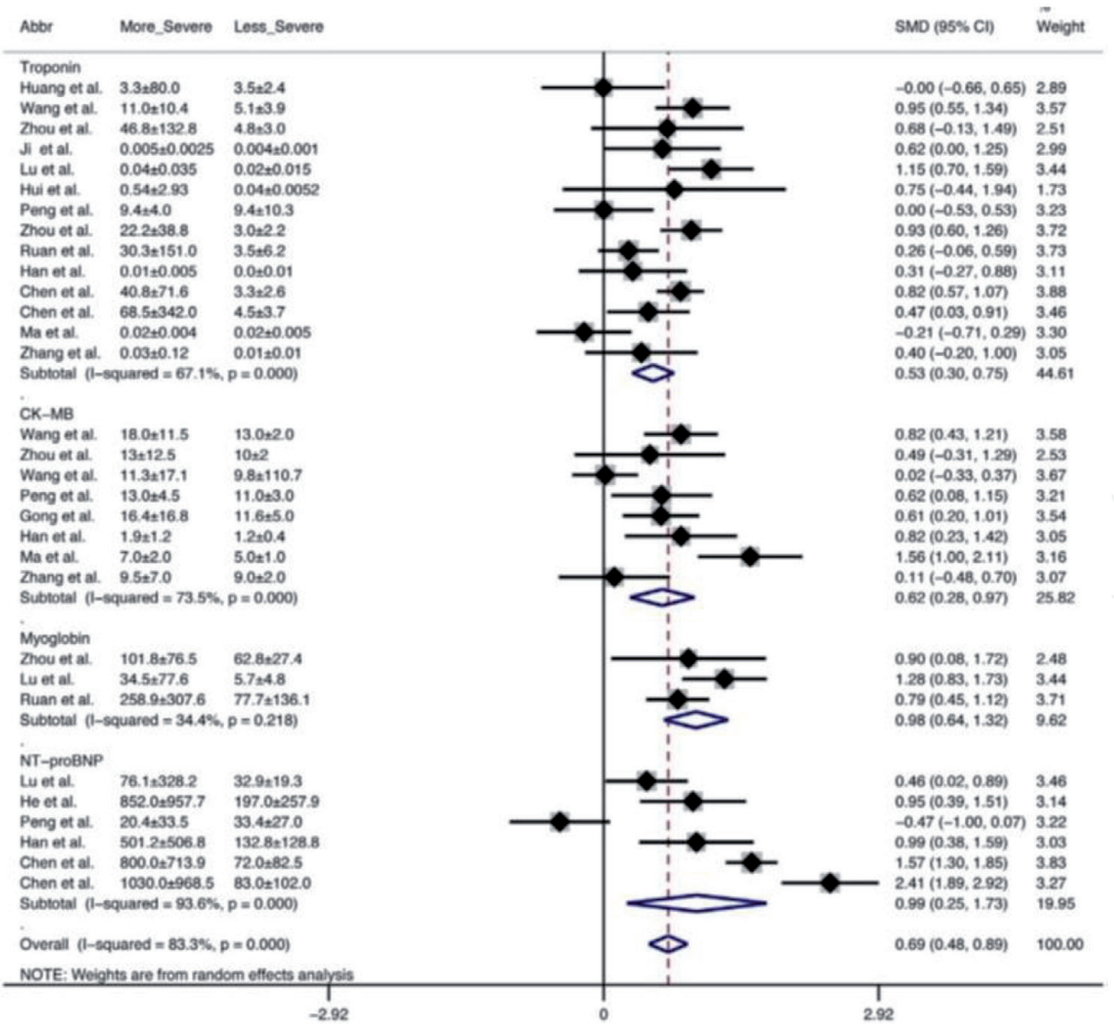

Figure 10.
Forest plot of cardiac biomarker standard mean difference between severe and less severe cases [source, Li et al. [53]].

related cardiac injury was more likely to die than those without (summary risk ratio 3.85 (95%CI 2.13 to 6.96, p = <0.001) [53].

With the emergence of cTn elevation in severe COVID-19 disease, attention turned to its prognostic value. A study of 416 COVID-19 patients by Shi and colleagues found elevated cTnI in 1 in 5 presenting patients, and positive cTn patients were more likely to require non-invasive ventilation and develop acute respiratory distress syndrome or acute kidney injury. In addition, the mortality rate was 10-fold higher in those patients with evidence of myocardial injury [43]. This is consistent with other studies.

Guo and colleagues reported 28% myocardial injury demonstrated by an elevated cTnT in 187 COVID-19 patients; with an in-hospital mortality of 60% and a higher incidence of mortality (69%) in those cTnT positive patients with underlying cardiovascular disease compared to 38% mortality in those without a cardiac history [55].

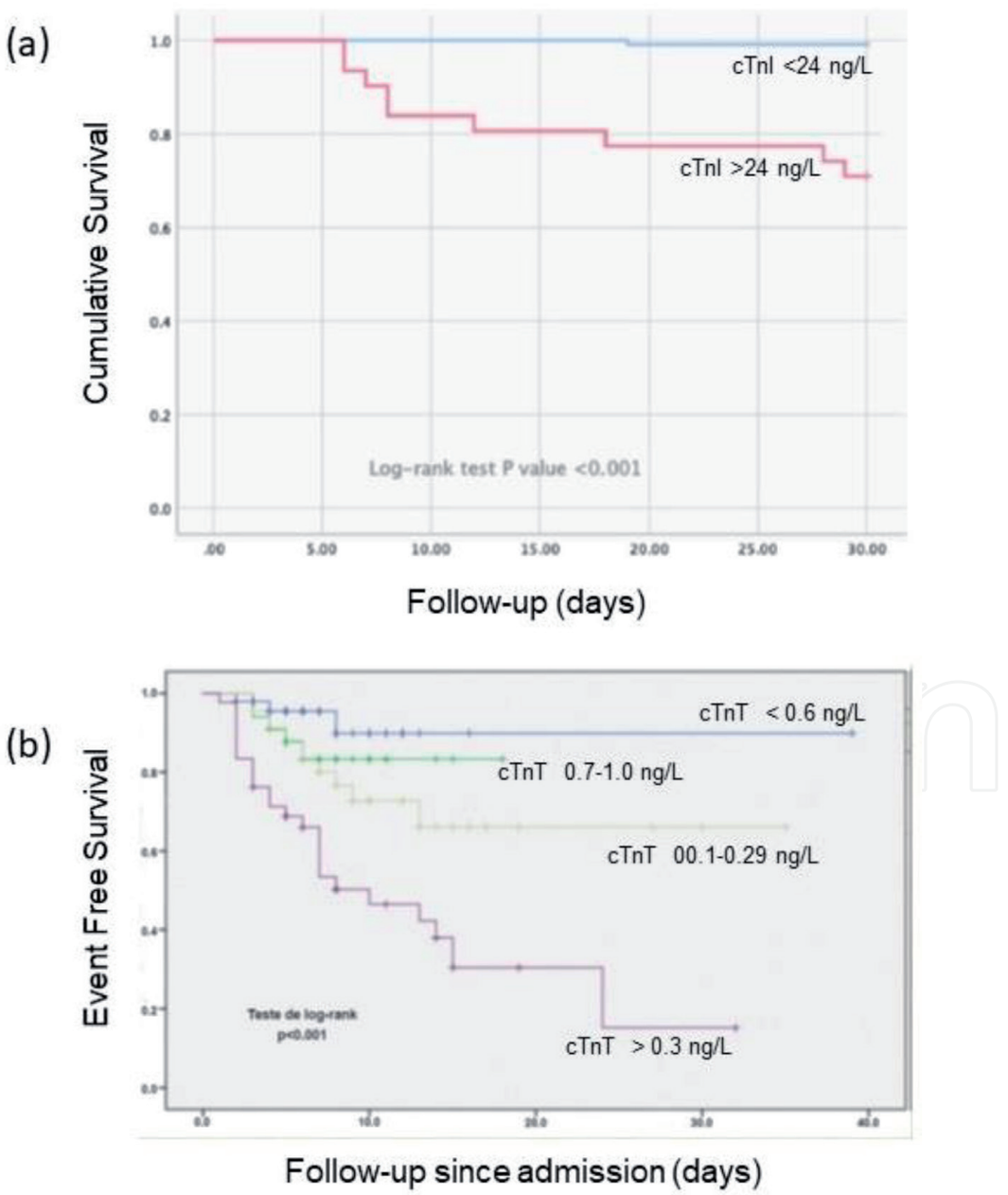

Figure 11.
Kaplan–Meier survival analysis of survival by (a) dichotomised cTnI over 40 days and by (b) cTnT quartiles over 30 days. [sources: Adapted from Cinar, et al. [61] and Almeida Jr. et al. [62] respectively].

Giustino and colleagues investigated 305 COVID-19 patients in 7 hospitals in New York City, USA and Milan, Italy. Patients exhibiting myocardial injury has elevated inflammatory markers, electrocardiographic abnormalities as well as transthoracic echocardiographic (TTE) evidence of left ventricular wall motion abnormalities, global left ventricular dysfunction, grade II or III left ventricular diastolic dysfunction, right ventricular dysfunction and pericardial effusion. In-hospital mortality was 32% in patients with myocardial damage and TT abnormalities, 19% with cTn positive myocardial injury only and 5% in those without evidence of cardiac involvement [56].

Lala and colleagues investigated the degree of myocardial injury in laboratory-confirmed cases of COVID-19 and correlated findings with outcome [57]. 36% of 2,736 patients had an elevated cTnI (>0.03 ng/mL).

Seven studies have investigated the prognostic value of elevated cTn in COVID-19. Five utilised cTnI [57–61], one cTnT [62] and one with combined cTnT and cTnI from different institutions [63]. In all cases, an elevated cTn (cTnI, **Figure 11a**; cTnT **Figure 11b**) was associated with poor outcome; be it in-hospital mortality, or combined endpoints of all-cause mortality and need for mechanical ventilation. Lala and colleagues [57] identified even minor elevations in cTnI (0.03 to 0.09 ng/ml) were associated with mortality (Hazard ratio 1.75; 95%CI = 1.37 to 2.24, $p < 0.001$). Those with greater cTnI concentrations above 0.09 ng/L conferred greater risk (Hazard ratio 3.03, 95% CI 2.42 to 3.80).

The underlying pathological mechanisms resulting in elevation in cTn in patients with COVID-19 have not been fully elucidated. The vast majority of reported cardiovascular complications in COVID-19 refer to acute cardiac injury, with an incidence of 8–22%. Other mechanisms (% incidence) include pulmonary thrombosis and arterial/venous thromboembolism (16–49%); chronic heart failure (52% in non-survivors, 12% in survivors); Acute coronary syndromes (44% with ST segment elevation myocardial infarction [STEMI]); arrhythmia (17% overall; 44% vs. 9% in severe and mild cases respectively). A few case reports have demonstrated myocarditis and pericardial disease [64].

9. Electrocardiographic and echocardiographic changes in COVID-19

The cardiac involvement in COVID-19 is diverse and as such varying different findings have been observed with diagnostic tools such as the electrocardiogram (ECG) and echocardiography. ECG changes in COVID-19 represent both left and right-sided heart disease [65] and are associated with a higher risk of mortality. In a study of 756 patients, 90 (12%) of which died (**Table 2**); one or more atrial premature contractions right bundle or intraventricular block, ischemic T-wave inversion and nonspecific repolarisation were associated with death [65]. These finding were

ECG Abnormality	Odds Ratio	95% CI
One or more atrial premature contraction	2.57	1.23 to 5.36
Right bundle branch or intraventricular block	2.61	1.32 to 5.18
Ischemic T-wave inversion	3.49	1.56 to 7.80
Nonspecific repolarisation	2.31	1.27 to 4.21

Table 2.
Odds ratio for ECG findings significantly associated with mortality. 95%CI, 95% confidence interval [source: McCullough et al. [65]].

further supported by De Vita and colleagues [66] who observed the ECG on admission was a helpful tool to identify COVID-19 patients with increased risk of death.

In a retrospective analysis of 319 severe and critically severe COVID-19 cases, Wang and colleagues observed 118 (37%) with normal ECG and 201 (63%) abnormal ECG traces. Differences were observed in ST-T changes, sinus tachycardia, atrial fibrillation, and atrial tachycardia between the group severity. Sinus tachycardia and atrial fibrillation were the independent risk factors of in-hospital death and ventilator use and could be used as an independent predictor of poor outcome [67].

A caveat to ECG induced changes is due to drug therapies given in severe COVID-19 infections. Drug-induced changes associated with chloroquine, hydroxychloroquine and azithromycin can result in a prolonged corrected QT (QTc), however such elongations do not induce arrhythmia-related death [68].

Echocardiographic findings demonstrate Left and right ventricular abnormalities in 39% and 33% of COVID-19 patients respectively [69]. severe ventricular dysfunction or tamponade is observed in approximately 15% of patients. In those without pre-existing cardiac disease the echocardiogram is abnormal in roughly half of COVID-19 patients with approximately 15% demonstrating severe disease. In a study of 90 hospitalised patients with severe (44, 49%) and non-severe (46, 51%) COVID-19; right ventricular (RV) and left ventricular (LV) functions were compared [70]. The RV and LV diameters were larger in severe patients compared to non-severe. Left ventricular ejection fraction (LVEF) were significantly ($p = <0.001$) lower (54.0% ±9.8%) in the severe-infections compared to the non-severe (61.9 ± 4.8%). Furthermore, pericardial effusions were observed in 23% of the severe patients with no observed cases in the non-severe patients.

In a study of 749 known COVID-19 positive patients undergoing transthoracic echocardiography (TTE), 38% were found to have LVEF ≤50% and 14% had moderately reduced right ventricular function. Stress-induced cardiomyopathy as evident by wall motion abnormalities were observed in four patients. A significant inverse relationship between cTnT and LVEF was observed ($P = -0.34$, $P = 0.006$). On the basis of the clinical TTE findings, therapeutic management was altered in 24% due to concern for a major cardiac even and in 14% where haemodynamic instability warranted TTE [71].

Both ECG and echocardiography are useful tools in the identification of left and right-sided cardiac dysfunction in COVID-19. Abnormalities are more frequent as infection severity increases and are often associated with poor prognosis.

10. Gross cardiac pathology and histopathology

A number of post-mortem (autopsy) studies have been performed on COVID-19 patients [72–79]. Four main pathological processes are generally observed: (a) Diffuse alveolar infiltration and damage with hyaline membrane formation, (b) thromboembolic disease in pulmonary and cardiac tissue and peripheral deep vein thrombosis, (c) hemophagocytes and (d) depletion of immune related cells [80, 81]. Gross cardiac examination (**Figure 12**) often reveals enlarged hearts [75, 76, 79] and the myocardium appears pale and flabby [76]. Thrombotic pathology is predominantly found in the lung, being present in 90% of cases; in 60% of hearts and 45% of kidneys [80].

In nine community deaths with suspected COVID-19 infections, Youd and colleagues did not observe any cases of myocarditis, however one case of bacterial bronchopneumonia had associated myocarditis. Contraction band necrosis was observed in a 86y Caucasian Male who had an underlying history of hypertension and cardiovascular disease. Cardiac amyloidosis was evident in one case [79].

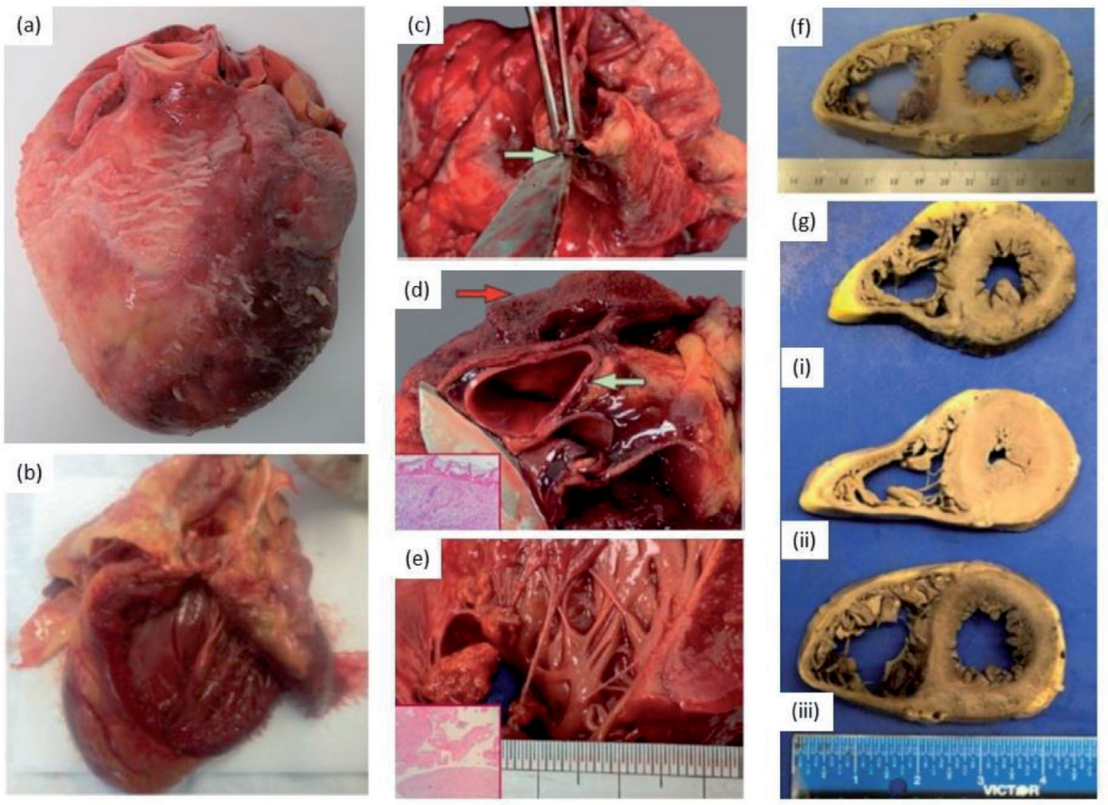

Figure 12.
Gross macroscopic cardiac pathology in COVID-19. (a) Fibrinous myocarditis; (b) cardiac hypertrophy with pale flabby myocardium; (c) macroscopic right coronary artery thrombosis (green arrow); (d) contained aortic dissection (green arrow) and fibrinous pericarditis (red arrow and H&E histology inset) in a 22y male; (e) gross marantic endocarditis with associated H&E histology inset; (f) extreme right ventricular dilatation with intraventricular septum straightening in a formalin fixed heart; (g) transverse sections demonstrating extensive right ventricular dilation of (i) 2.9:1.7 cm, (ii) 4.0:0.9 cm, (iii) 3.6:3.4 cm. [sources: Adapted from Youd et al. [79], Hanley et al. [80], Fox et al. [82, 83]].

An Italian study of 22 autopsies (18 with comorbid conditions, 4 without) demonstrated significant pulmonary and cardiovascular pathologies. All 22 deaths were reported as cardiorespiratory failure [76]. Cardiovascular pathologies are reported in **Table 3**.

A systematic review of histopathological findings by physiological system have identified cardiovascular findings such as focal lymphocytic inflammation, acute cardiomyocyte necrosis, presence of inflammatory cells and apoptotic bodies [74].

A multicentre study of 21 autopsy examinations by Basso and colleagues [73] examined cardiac tissue. Lymphocytic myocarditis was present in 3 (14%) cases, two of which were CD4 predominant T-cells, and one CD8 prominent. 86% of cases demonstrated interstitial macrophage infiltration. Mild pericarditis was evident in 4 cases. Common histological findings from cardiac tissue are presented in **Figure 13**.

Although the underlying mechanisms of cardiac involvement in COVID-19 infection remain to be fully elucidated, cardiac fibrosis occurs in tandem with local and systemic inflammatory responses [84]. Whilst these mechanisms are designed to facilitate healing following tissue damage, an excess of the inflammatory response along with the development of fibrotic tissue are pathological drivers for global organ damage. Overt inflammation and fibrosis in the heart can result in abnormal cardiac remodelling potentiating the development of acute and chronic heart failure. Anti-inflammatory and anti-fibrotic therapies are in general unsuccessful in improving damaged cardiac tissue function. With respect to COVID-19,

Histopathological findings	COVID-19 deaths with comorbid conditions (n = 18) (%)	COVID-19 deaths without comorbid conditions (n = 4) (%)
Myocarditis	9 (50.0)	3 (75.0)
Vasculitis	5 (27.8	3 (75.0)
Inflammatory infiltrate	13 (72.3)	3 (75.0)
Focal necrosis	6 (33.4)	2 (50.0)
Pericarditis	9 (50.0)	4 (100)
Vascular fibrosis	4 (22.3)	2 (50.0)

Table 3.
Cardiovascular histopathological findings in COVID-19 cadavers with and without comorbid conditions [source: Falasca et al. [76]].

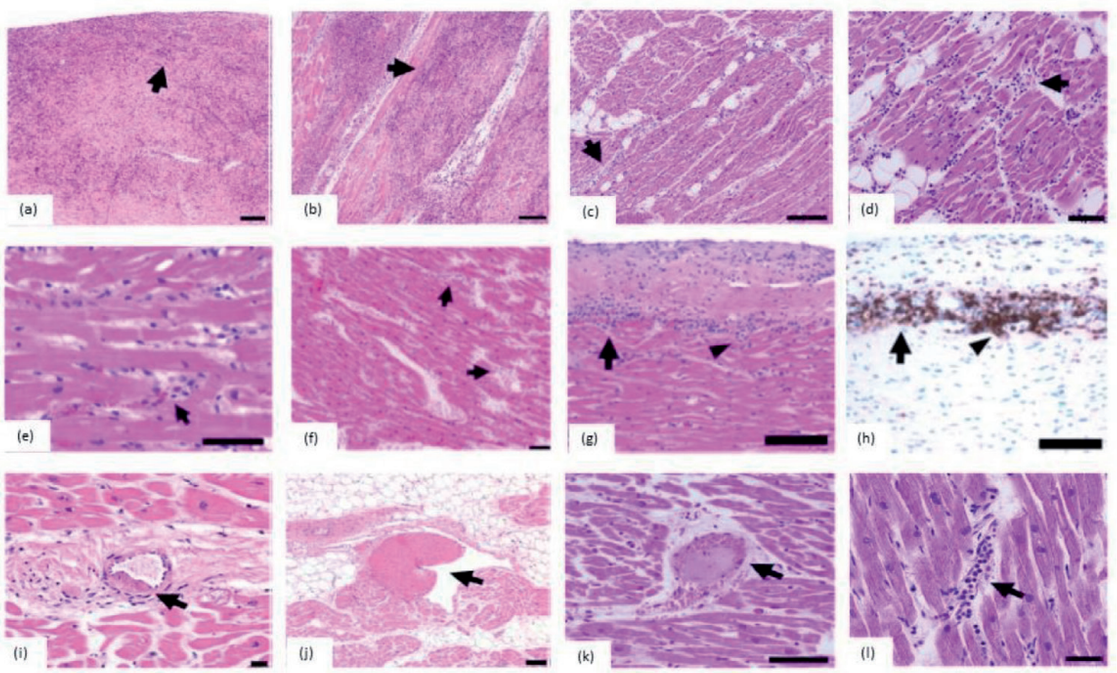

Figure 13.
(a and b) Myocarditis. Biventricular multifocal and diffuse lymphocytic myocarditis (arrows) with extensive myocyte injury and previously undiagnosed cardiac amyloidosis (H&E) x50 in an 86y male; (c and d) Biventricular multifocal lymphocytic myocarditis (arrows) with myocyte injury (H&E x100). Atrial fibrillation developed 2 d before death, 64y male; (e) Increased interstitial macrophage H&E x400) in a 60y male; (f) Increased macrophage cells within the myocardial interstitum (H&E x100) in a 73y female; (g) Focal lymphocytic pericarditis (arrows, H&E, x400) comprised of (h) CD8+ lymphocytes associated with focal myocardial inflammation in the absence of myocyte injury (arrowhead, CD8 immunostaining x400); (I and j) Small vessel changes. Microthrombus in a small myocardial artery (a, arrow H&E x100) and organised venous thrombosis (b, arrow H&E x100) in a 70y male; (k) Thrombus in a small myocardial vein (arrow, H&E x200) in a 71y male; (l) Leucocyte aggregates of eosinophils and mononuclear cells in capillaries and small veins (arrow, H&E x400) in a 64y male.[Source: Adapted from Basso et al., [73]].

further work is required to identify potential therapeutic targets of regulation and moderation of cardiac fibroblast function and thus reduce the burden of inflammatory-responsive fibrotic-based heart failure.

11. Conclusion

The novel Coronavirus disease, COVID-19 that emerged just over one year ago has caused substantial disruption to everyday life for every human on the

planet. In the ensuing year, science and medicine have fought a race against time to understand the aetiology and pathogenicity of the disease. The overriding signs and symptoms supported by diagnostic testing indicates diffuse alveolar infiltration with vascular thromboembolic involvement in pulmonary, cardiac and renal tissue. Cardiac electrocardiography, echocardiography and cardiac biomarker testing are vital in the identification and management of patients with COVID-19 and concomitant cardiovascular involvement. Pathological findings at autopsy aid in the understanding of the pathophysiology of cardiovascular involvement in the disease. With the development of vaccines and mass vaccination programmes for the vulnerable along with herd immunity in the young, the global population will survive this novel pandemic but to significant cost both socially, economically and emotionally.

Author details

David C. Gaze
School of Life Sciences, University of Westminster, London, United Kingdom

*Address all correspondence to: d.gaze@westminster.ac.uk

References

[1] Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed. 2020 03 19,;91(1):157-60.

[2] WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. []. Available from: www.covid19.who.int.

[3] Wise J. Covid-19: New coronavirus variant is identified in UK. BMJ. 2020 December 16;371:m4857.

[4] European Centre for Disease Prevention and Control. Risk related to spread of new SARS-CoV-2 variants of concern in the EU/EEA. 2020 29 December.

[5] Conti P, Caraffa A, Gallenga CE, Kritas SK, Frydas I, Younes A, et al. The British variant of the new coronavirus-19 (Sars-Cov-2) should not create a vaccine problem. J Biol Regul Homeost Agents. 2021 February 24;35(1):3.

[6] Peiris JSM, Yuen KY, Osterhaus ADME, Stöhr K. The severe acute respiratory syndrome. The New England journal of medicine. 2003 Dec 18,;349(25):2431-2441.

[7] Yao H, Song Y, Chen Y, Wu N, Xu J, Sun C, et al. Molecular architecture of the SARS-CoV-2 virus. Cell. 2020 October 29,;183(3):730,738.e13.

[8] Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. Cell (Cambridge). 2020 May 14,;181(4):894,904.e9.

[9] Balakumar P, Jagadeesh G. A century old renin-angiotensin system still grows with endless possibilities: AT1 receptor signaling cascades in cardiovascular physiopathology. Cell Signal. 2014 Oct;26(10):2147-2160.

[10] Gonzalez NC, Allen J, Schmidt EJ, Casillan AJ, Orth T, Wood JG. Role of the renin-angiotensin system in the systemic microvascular inflammation of alveolar hypoxia. Am J Physiol Heart Circ Physiol. 2007 May 01;292(5):2285.

[11] Lin C, Huang Y. Does the direct renin inhibitor have a role to play in attenuating severity of the outbreak coronavirus disease 2019 (COVID-19)?: Therapeutic Advances in Endocrinology and Metabolism. 2020 April 16,.

[12] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004 June 01;203(2):631-637.

[13] Bos JM, Hebl VB, Oberg AL, Sun Z, Herman DS, Teekakirikul P, et al. Marked up-regulation of ACE2 in hearts of patients with obstructive hypertrophic cardiomyopathy: Implications for SARS-CoV-2-mediated COVID-19. Mayo Clin Proc. 2020 July 01;95(7):1354-1368.

[14] Banu N, Panikar SS, Leal LR, Leal AR. Protective role of ACE2 and its downregulation in SARS-CoV-2 infection leading to macrophage activation syndrome: Therapeutic implications. Life sciences (1973). 2020 Sep 1,;256:117905.

[15] Li H, Wang Y, Ji M, Pei F, Zhao Q, Zhou Y, et al. Transmission Routes Analysis of SARS-CoV-2: A Systematic Review and Case Report. Front Cell Dev Biol. 2020 -7-10;8.

[16] Fennelly KP. Particle sizes of infectious aerosols: Implications for infection control. The lancet respiratory medicine. 2020 Sep;8(9):914-924.

[17] Jones NR, Qureshi ZU, Temple RJ, Larwood JPJ, Greenhalgh T, Bourouiba L. Two metres or one: what is the evidence

for physical distancing in covid-19? BMJ. 2020 08 25,;370:m3223.

[18] Hindson J. COVID-19: Faecal–oral transmission? Nature reviews. Gastroenterology & hepatology. 2020 Mar 25,;17(5):259.

[19] Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Nature medicine. 2020 Mar 13,;26(4):502-505.

[20] Benton SC, Fraser CG. Faecal immunochemical tests in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration – Can a repeat test be used? Ann Clin Biochem. 2020 October 5,:0004563220967569.

[21] Kayaaslan B, Korukluoglu G, Hasanoglu I, Kalem A, Eser F, Akinci E, et al. Investigation of SARS-CoV-2 in semen of patients in the acute stage of COVID-19 infection. Urologia internationalis. 2020 Sep;104(9-10): 678-683.

[22] Holtmann N, Edimiris P, Andree M, Doehmen C, Baston-Buest D, Adams O, et al. Assessment of SARS-CoV-2 in human semen—a cohort study. Fertil Steril. 2020 -8;114(2):233-8.

[23] Schwartz DA. An Analysis of 38 Pregnant Women With COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. Arch Pathol Lab Med. 2020 /07/01;144(7):799-805.

[24] Schwartz DA, Dhaliwal A. Infections in Pregnancy With COVID-19 and Other Respiratory RNA Virus Diseases Are Rarely, If Ever, Transmitted to the Fetus: Experiences With Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, and Influenza. Arch Pathol Lab Med. 2020 /08/01;144(8):920-8.

[25] Kotlyar AM, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, et al. Vertical transmission of coronavirus disease 2019: a systematic review and meta-analysis. Am J Obstet Gynecol. 2020 -7-31.

[26] Rothan HA, Byrareedy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity. 2020 May;109:102433.

[27] Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. Journal of Medical Virology;n/a(n/a).

[28] Stephanie S, Shum T, Cleveland H, Challa SR, Herring A, Jacobson FL, et al. Determinants of Chest X-Ray Sensitivity for COVID- 19: A Multi-Institutional Study in the United States. Radiology: Cardiothoracic Imaging. 2020 September 24,;2(5):e200337.

[29] Cozzi A, Schiaffino S, Arpaia F, Della Pepa G, Tritella S, Bertolotti P, et al. Chest x-ray in the COVID-19 pandemic: Radiologists' real-world reader performance. European journal of radiology. 2020 Nov;132:109272.

[30] Pereira RM, Bertolini D, Teixeira LO, Silla CN, Costa YMG. COVID-19 identification in chest X-ray images on flat and hierarchical classification scenarios. Computer methods and programs in biomedicine. 2020 Oct;194:105532.

[31] Salameh J, Leeflang MM, Hooft L, Islam N, McGrath TA, Pol CB, et al. Thoracic imaging tests for the diagnosis of COVID-19. Cochrane Database of Systematic Reviews. 2020(9).

[32] Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, Zhang N, et al. Chest CT findings in coronavirus Disease-19 (COVID-19): Relationship to duration of

infection. Radiology. 2020 Feb 20,;295(3):200463.

[33] Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Letters. 2002 December 4,;532(1):107-110.

[34] Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Science. 2020 March 27;367(6485):1444-1448.

[35] Yang L, Tu L. Implications of gastrointestinal manifestations of COVID-19. The Lancet Gastroenterology & Hepatology. 2020 /07/01;5(7):629-30.

[36] Mao R, Qiu Y, He J, Tan J, Li X, Liang J, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: A systematic review and meta-analysis. The lancet. Gastroenterology & hepatology. 2020 Jul;5(7):667-678.

[37] Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal Influenza Infections and Cardiovascular Disease Mortality. JAMA Cardiol. 2016 06 01,;1(3):274-81.

[38] Alhogbani T. Acute myocarditis associated with novel middle east respiratory syndrome coronavirus. Ann Saudi Med. 2016 Jan-Feb;36(1):78-80.

[39] Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, et al. Cardiac complications in patients with community-acquired pneumonia: A systematic review and meta-analysis of observational studies. PLoS Med. 2011 Jun;8(6):e1001048.

[40] Yu C, Wong RS, Wu EB, Kong S, Wong J, Yip GW, et al. Cardiovascular complications of severe acute respiratory syndrome. Postgrad Med J. 2006 Feb;82(964):140-144.

[41] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. JAMA. 2020 -3-17; 323(11):1061-9.

[42] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 02 15,;395(10223):497-506.

[43] Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. JAMA Cardiol. 2020 07 01,;5(7):802-10.

[44] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 03 28,;395(10229):1054-62.

[45] Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, et al. Association of Troponin Levels with Mortality in Italian patients hospitalized with coronavirus disease 2019: Results of a multicenter study. JAMA Cardiol. 2020 August 26.

[46] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA. 2020 04 28,;323(16):1574-81.

[47] Akbariqomi M, Hosseini MS, Rashidiani J, Sedighian H, Biganeh H, Heidari R, et al. Clinical characteristics and outcome of hospitalized COVID-19 patients with diabetes: A single-center, retrospective study in Iran. Diabetes research and clinical practice. 2020 Nov;169:108467.

[48] Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R,

Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: Prospective observational cohort study. BMJ. 2020;369:m1985.

[49] Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, et al. Clinical characteristics of Covid-19 in new York City. New England Journal of Medicine. 2020 June 11,;382(24):2372-2374.

[50] Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Acute myocardial injury in patients hospitalized with COVID-19 infection: A review. Progress in Cardiovascular Diseases. 2020 June 6,.

[51] Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020 03 26,;368:m1091.

[52] Gaze DC. Clinical utility of cardiac troponin measurement in COVID-19 infection. Ann Clin Biochem. 2020 May 01;57(3):202-205.

[53] Li J, Han T, Woodward M, Anderson CS, Zhou H, Chen Y, et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis. Prog Cardiovasc Dis. 2020 Jul - Aug;63(4):518-24.

[54] Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis. 2020 June 01;63(3):390-391.

[55] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 07 01,;5(7):811-8.

[56] Giustino G, Croft LB, Stefanini GG, Bragato R, Silbiger JJ, Vicenzi M, et al. Characterization of myocardial injury in patients with COVID-19. J Am Coll Cardiol. 2020 November 03;76(18):2043-2055.

[57] Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and Impact of Myocardial Injury in Patients Hospitalized With COVID-19 Infection. J Am Coll Cardiol. 2020 -08-04;76(5):533-46.

[58] Al Abbasi B, Torres P, Ramos-Tuarez F, Dewaswala N, Abdallah A, Chen K, et al. Cardiac troponin-I and COVID-19: A prognostic tool for In-hospital mortality. Cardiol Res. 2020 December 01;11(6):398-404.

[59] Shah P, Doshi R, Chenna A, Owens R, Cobb A, Ivey H, et al. Prognostic value of elevated cardiac troponin I in hospitalized Covid-19 patients. Am J Cardiol. 2020 August 28.

[60] Cordeanu EM, Duthil N, Severac F, Lambach H, Tousch J, Jambert L, et al. Prognostic value of troponin elevation in COVID-19 hospitalized patients. J Clin Med. 2020 December 17;9(12):10.3390/jcm9124078.

[61] Cinar T, Hayiroglu MI, Cicek V, Kilic S, Asal S, Dogan S, et al. Prognostic significance of cardiac troponin level in Covid-19 patients without known cardiovascular risk factors. Am J Emerg Med. 2020 December 18.

[62] Almeida Junior, G L G, Braga F, Jorge JK, Nobre GF, Kalichsztein M, Faria PMP, et al. Prognostic value of troponin-T and B-type natriuretic peptide in patients hospitalized for COVID-19. Arq Bras Cardiol. 2020 October 01;115(4):660-666.

[63] Schiavone M, Gasperetti A, Mancone M, Kaplan AV, Gobbi C, Mascioli G, et al. Redefining the prognostic value of high-sensitivity

troponin in COVID-19 patients: The importance of concomitant coronary artery disease. J Clin Med. 2020 October 12;9(10):10.3390/jcm9103263.

[64] Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, et al. COVID-19 pandemic and troponin: Indirect myocardial injury, myocardial inflammation or myocarditis? Heart. 2020 August 01;106(15):1127-1131.

[65] McCullough SA, Goyal P, Krishnan U, Choi JJ, Safford Mokika M, Okin Peter M. Electrocardiographic findings in coronavirus Disease-19: Insights on mortality and underlying myocardial processes. Journal of cardiac failure. 2020 Jul;26(7):626-632.

[66] De Vita A, Ravenna SE, Covino M, Lanza O, Franceschi F, Crea F, et al. Electrocardiographic Findings and Clinical Outcome in Patients with COVID-19 or Other Acute Infectious Respiratory Diseases. J Clin Med. 2020 -11-12;9(11).

[67] Wang Y, Chen L, Wang J, He X, Huang F, Chen J, et al. Electrocardiogram analysis of patients with different types of COVID-19. Annals of Noninvasive Electrocardiology. 2020;25(6):e12806.

[68] Mehraeen E, Seyed Alinaghi SA, Nowroozi A, Dadras O, Alilou S, Shobeiri P, et al. A systematic review of ECG findings in patients with COVID-19. Indian Heart J. 2020 December 01;72(6):500-507.

[69] Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. European Heart Journal - Cardiovascular Imaging. 2020 September 1,;21(9):949-58.

[70] Barman HA, Atici A, Tekin EA, Baycan OF, Alici G, Meric BK, et al. Echocardiographic features of patients with COVID-19 infection: A cross-sectional study. Int J Cardiovasc Imaging. 2020 October 08.

[71] Jain SS, Liu Q, Raikhelkar J, Fried J, Elias P, Poterucha TJ, et al. Indications for and Findings on Transthoracic Echocardiography in COVID-19. J Am Soc Echocardiogr. 2020 -10;33(10):1278-84.

[72] Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. Am J Clin Pathol. 2020 May 05;153(6):725-733.

[73] Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal, A C, Aubry MC, et al. Pathological features of COVID-19-associated myocardial injury: A multicentre cardiovascular pathology study. Eur Heart J. 2020 October 14;41(39):3827-3835.

[74] Deshmukh V, Motwani R, Kumar A, Kumari C, Raza K. Histopathological observations in COVID-19: A systematic review. J Clin Pathol. 2020 August 18.

[75] Elsoukkary SS, Mostyka M, Dillard A, Berman DR, Ma LX, Chadburn A, et al. Autopsy findings in 32 patients with COVID-19: A single-institution experience. Pathobiology. 2020 September 17:1-13.

[76] Falasca L, Nardacci R, Colombo D, Lalle E, Di Caro A, Nicastri E, et al. Postmortem findings in Italian patients with COVID-19: A descriptive full autopsy study of cases with and without comorbidities. J Infect Dis. 2020 November 09;222(11):1807-1815.

[77] Sperhake J. Autopsies of COVID-19 deceased? Absolutely! Leg Med (Tokyo). 2020 -11;47:101769.

[78] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 April 01;8(4):420-422.

[79] Youd E, Moore L. COVID-19 autopsy in people who died in community settings: The first series. J Clin Pathol. 2020 December 01;73(12):840-844.

[80] Hanley B, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, et al. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: A post-mortem study. The Lancet Microbe. 2020 Oct;1(6):e245-e253.

[81] Maiese A, Manetti AC, La Russa R, Di Paolo M, Turillazzi E, Frati P, et al. Autopsy findings in COVID-19-related deaths: A literature review. Forensic Sci Med Pathol. 2020 October 07.

[82] Fox SE, Akmatbekov A, Harbert JL, Li G, Quincy Brown J, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: An autopsy series from New Orleans. Lancet Respir Med. 2020 July 01;8(7):681-686.

[83] Fox SE, Li G, Akmatbekov A, Harbert JL, Lameira FS, Brown JQ, et al. Unexpected features of cardiac pathology in COVID-19 infection. Circulation. 2020 September 15;142(11):1123-1125.

[84] Smolgovsky S, Ibeh U, Tamayo TP, Alcaide P. Adding insult to injury - Inflammation at the heart of cardiac fibrosis. Cell Signal. 2021 -01;77:109828.