Review Article

Fatality in COVID 19: an overview of causes of death and organ involvement

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ABSTRACT

COVID-19 is a viral infectious disease caused by the SARS CoV-2 virus, which is a respiratory pathogen. It originated in the city of Wuhan in China from where it spread throughout the world. This virus causes severe respiratory distress in a certain number of patients with specific risk factors. In our article, authors plot the route from the onset of the disease to its progress to death in patients, and determine the most likely causes that lead to such a poor prognosis. Authors also evaluate the severity and extent of organ damage that is involved and associated with fatality in cases with COVID-19. Authors also aim for clinicians to better understand and perceive the circumstances under which a patient may progress from severe infection towards death, and manage such cases in a more efficient manner.

Keywords: ARDS, Cause of death, COVID-19, Coronavirus, SARS CoV-2, Organ involvement, Pandemic, Post-mortem

INTRODUCTION

COVID-19 refers to the disease caused in humans due to contraction of the Novel Human Coronavirus (Severe Acute Respiratory Syndrome CoV-2) which is established to be a respiratory pathogen. In human hosts, it causes symptoms that vary from Dry Cough and fever to ARDS induced respiratory failure. This virus is of zoonotic origin, which essentially means that it started with an animal to human transmission or jumping. This puts into context its place of origin, which was early in December 2019 in the Wuhan Live Seafood Market, in the Hubei province of China, where trading of live animals including exotic mammals ran rampant and unchecked.

On analysis, this new virus shows less severity than its close cousin SARS, but the transmissibility is far greater. As of March 31, 2020, 18:12 GMT, there were a total of

837,115 confirmed cases and 41,249 deaths, which put the mortality rate at about 4.92%. This far exceeds the number of cases and deaths reported in the SARS and MERS outbreaks in 2003 and 2012 respectively. However, the case fatality rate of both SARS and MERS heavily exceed that of COVID-19.¹ This goes on to establish the fact that what SARS and MERS lack in transmissibility, make up for in severity. In India, on the same date and time as mentioned above, the total number of active cases stand at 1238 and 35 deaths are reported, which puts the mortality rate for the country at 2.74%.¹

The most abundantly found HCoVs that are pathogens in the human body are 229E, OC43, NL63 and HKU 1. The former two accounted for majority of the human respiratory pathogens exhibiting relatively decreased virulence. Pyroptosis, a novel form of inflammatory cell death, is a possible mechanism for the increased virulence of SARS CoV-2.

SARS CoV-2 pathogen shows behavioral, clinical and genomic similarities to the SARS CoV pathogen involved in the SARS outbreak of 2003. CoVs are RNA viruses that are non-segmented, positive sense and single strand. This has the largest known genome among RNA viruses. Most related members of the Coronaviridae family within the order Nidovirales, show the presence of 4 major structural proteins:

- Spike surface glycoproteins,
- Small envelope protein,
- Matrix protein, and
- Nucleocapsid protein.²

The protein of our interest happens to be the 'Spike surface glycoproteins' that bind to the ACE-II (Angiotensin Converting Enzyme - II) receptors on the cell surface, via receptor binding domains. These receptors are present throughout the human body, but is present in highest concentrations in certain organ systems, which in the decreasing order of number of receptors are The Respiratory System, The Gastrointestinal System, The Lymphatic System, The Thymus, Bone Marrow, Spleen, Liver, Kidneys and The Brain.²

There is abundant research and data about COVID-19 epidemiology, pathology, clinical features and case fatality. In this article, authors attempt to review this information and deduce the major remarkable features regarding the post-mortem findings of COVID-19 which help determine the various causes of deaths and the extent to which the various organ systems are affected. This will facilitate better understanding of this often fatal condition.

REVIEW OF LITERATURE

Clinical features

As authors have already established, all SARS, MERS and COVID-19 vary significantly in their severity. However, all three present with the same spectrum of symptomatic changes that begin with flu-like symptoms and escalate to ARDS in severe cases. The clinical manifestations in the case of COVID-19 show a fairly consistent pattern without much variation over age and genders. These manifestations include: Fever, Dry Cough, Dyspnoea, Fatigue, Chest Pain/Discomfort, Anosmia, Dysgeusia and Sputum Production. Less common symptoms include Headache, Sore throat, Rhinorrhea, Nausea and Diarrhoea. Palpitations have been reported in a number of cases, however, it isn't as rampant as the other symptoms and therefore is hardly mentioned.³

The virus shows an incubation period of 3-7 days and may typically extend up to 14 days in some cases. However, there have been reports of asymptomatic viral shedding for as long as 39 days in some rare cases.

Transmission occurs majorly through respiratory droplets that are transmitted by means of aerosol transmission and personal contact. The respiratory droplets from an infected person can travel a distance of up to 3 feet in all directions. These respiratory droplets tend to get deposited on the mucous membranes of eyes, nose and mouth. It is interesting to note that, according to recent studies, the virus can gain entry into the body even through the ocular surface and there have been reports suggesting transmission through an infected person's excreta.³ Research teams have devised methods to test a city's sewage and drainage outflow to determine the presence of the virus in its population.

The fatality of cases with COVID-19 are heavily dependent upon underlying health conditions and the most common co-morbidities include Hypertension, Diabetes, Cardiac Conditions and Immunocompromised status. However, none of these conditions reflect absolute mortality, as several patients with these health conditions have successfully recovered and been discharged.

A common pattern observed in all fatal outcomes was the presence of either 'chronic bronchitis' or 'Coronary Heart Disease' and this puts into context two common features exhibited by most patients before deaths, which were respiratory failure and Bradycardia. Various other comorbidities include, but are not limited to ARDS, anemia, acute Cardiac Injury and secondary infection.⁴

Thorough analysis of cases that progressed to death is integral to creating better management strategies and is a public health priority as of now. Old age stands out to be another factor heavily influencing the mortality in COVID-19 cases, although it is not an indicator of absolute mortality as patients over 100 years of age have successfully recovered and been discharged. The most critical cases show a progression to conditions like ARDS, septic shock, metabolic acidosis, and coagulation dysfunction. Most cases that progressed to death were of patients that died of multiple organ failure.⁴

There is no sufficient evidence that might link fever and cough to mortality, but development of dyspnea strongly indicates the requirement of intensive intervention and patients may exhibit low survivability.

In terms of comorbidities, Hypertension takes the top spot, with patients with it being most likely to get COVID-19. However, patients with diabetes are most at risk for fatal outcomes and have a poor prognosis. Another remarkable pattern emerging from recent studies is that the severity of pre-existing Cardiovascular and Cerebrovascular conditions is inversely proportional to the time it takes for them to progress from hospital admission to death. However, the proportion of patients that progress to death is significantly less in cases of pre-existing Cardiovascular, Cerebrovascular and pulmonary conditions in comparison to other comorbidities mentioned.⁴

Lab diagnosis

Laboratory findings indicate that the disease progression is divided into three phases. This includes an early phase, a middle phase and a late/severe phase. In the early phase, leukocytes, including lymphocytes are either normal or decreased and procalcitonin remains normal. However, in the later stages there is an ultimate increase in the WBC count. Muscular and liver enzyme levels along with myoglobin are increased and so is the case with CRP, ESR and D-dimer. Peripheral blood lymphocyte count is considerably low. The SARS CoV-2 nucleic acid can be detected in throat, sputum, lower respiratory tract secretions and blood. Alanine aminotransferase (ALT), Lactate Dehydrogenase (LDH), Cardiac Troponin-I, Creatine Kinase, Serum Ferritin and InterLeukin-6 (IL-6) are some lab findings that may be deviated from their normal values, but cannot be determined in emergency conditions.²

Imaging

Abnormal findings in CT are reported with bilateral pneumonia, and bilateral multiple lobular and sub-segmental areas of consolidation, which is much more prominent in the lower lobes. The consolidation becomes more prominent over time, especially before death. Subsequent chest CT images showed bilateral ground glass opacities consistent with ARDS. The radiographic findings are very much consistent with the patterns seen in SARS and MERS epidemics, but the bilateral lung involvement is a novel feature, characteristic of COVID-19. Lymphadenopathy, Cavitation, Pulmonary nodules and Pleural effusion are not reported in cases of COVID-19 and Pneumothorax is reported very rarely, if ever, but cannot be associated as a complication of the viral infection.²

Causes of death and organ involvement

In this section, authors shall attempt at identifying and establishing the underlying conditions and their further developments during the course of COVID-19 that may be the major cause of fatalities in these cases. Authors may identify the most probable casualties by the following characteristic markers:

- Older age
- Comorbidities, like Diabetes and Hypertension
- Increased D-dimer levels
- Signs of sepsis on admission
- Extensive use of ventilation, which is non-invasive in nature.

Certain specific markers may allow us to quickly identify patients with poor prognosis at an early stage of their treatment course. These are older age, increased SOFA (Sequential Organ Failure Assessment) score and increased D-dimer ($>1\mu\text{g/mL}$). SOFA, previously called Sepsis related organ failure assessment score, assesses the

rate of organ failure in ICU. High levels of D-dimer indicate increased risk of abnormal blood clotting such as Deep Vein Thrombosis (DVT). Increased rates of respiratory failure, sepsis and secondary infection is seen in the patients that develop fatal complications. Old age leads to rampant inflammation throughout the major organ systems and weakening of the immune system, which promotes viral replication and organ damage. In the patients that progressed to death, viral RNA could be detected until the day of death and antiviral treatment couldn't mitigate the viral shedding from such patients. Long term isolation strategies and antiviral therapies are determined by analyzing the prolonged viral shedding. However, accurate duration of viral shedding cannot be determined due to inadequate genetic material.^{5,6}

In a study conducted by JAMA Internal Medicine, 40% of patient population with severe COVID-19 infection developed ARDS, and 50% of those cases died due to the disease. American Lung Association says, ARDS, initially diagnosed as pneumonia or pulmonary edema, is a rapidly progressive disease that can occur in critically ill patients with presence of symptoms such as shortness of breath, cough, fever, increased heart rate and shallow breathing along with chest pain during inhalation. The SARS CoV-2 virus enters the lungs and causes damage to the cells leading to inflammation of the lung vasculature. This causes insufficient gaseous exchange leading to severe hypoxia. In the later stages, the lung is already severely damaged, and the body tries to fend off the infection by sending immune cells to the point of infection.

This causes an exaggerated inflammatory reaction, which adversely affects the ability of the lung to perform gaseous exchange. Thus, ARDS in COVID-19 is less directly caused due to the virus itself, and mostly due to the inflammatory reaction caused by the immune cells trying to fight the infection. In order to fight off the SARS CoV-2 pathogen, the body generates an overactive immune response. This toxic response leads to tissue damage, Multiple Organ Failure and death. This is characterized by a drop in blood pressure with increased heart rate, fever, rapid heavy breathing, sudden confusion and systemic illness.⁴ The primary cause of death in COVID-19 is respiratory failure. While lungs are the major site of infection, brain can also be infected in some patients. Although very little is known about the pathogenesis of SARS CoV-2 in brain, the virus may lead to acute cerebral vascular diseases and severely ill patients are most vulnerable to neurological injuries. Thus, it is essential to closely monitor all facets of possible infections to better manage the disease.⁷

Post mortem findings

It is imperative for the medical fraternity to solicit every bit of knowledge they can from the post mortem analyses that have been conducted on the deceased COVID-19 cases.

This will not only assist us in better treatment and management of severely ill patients, but also allow us to better guess the possible causes associated with fatal outcomes. Thus, authors consider it absolutely imminent that authors include our understanding of the post-mortem findings in our resource.²

Gross findings

Pathological findings are likely to be in the chest and may include pleurisy, pulmonary edema, pericarditis, and lung consolidation. Lungs will be heavier than usual. In a comparative analysis, it was found that the pulmonary fibrosis and Consolidation will be less severe than SARS. However, the exudative reaction seen is much more evident than in the aforementioned infection. Secondary infection may be found superimposed on viral infection, leading to purulent inflammation.²

Microscopic findings

In most of the cases authors reviewed, Needle Core Biopsies were performed post-mortem, with the necessary permissions from the next of kin, and the results of our interest arise from three major organs, namely Lungs, Liver and Heart.

Lungs

- Alveolar damage due to epithelial cell injury.
- Hyaline membrane formation.
- Edema.
- Type-ii pneumocyte hyperplasia.
- Focal inflammation.
- Multinucleated giant cell formation without hyaline membrane.
- Consolidation by fibroblastic proliferation w extracellular membrane and fibrin forming clusters. It also includes intra-alveolar neutrophilic infiltration consistent with superimposed bacterial bronchopneumonia.

Liver

- Mild lobular infiltration by small lymphocytes and centrilobular sinusoidal dilatation.
- Patchy necrosis
- Microvesicular steatosis

Heart

- Focal mild fibrosis.
- Mild myocardial hypertrophy.
- Changes related to the underlying condition.²

Post-mortem CT (PMCT) findings

- Ground-glass lung opacities or mixed ground glass and consolidation.
- Vascular enlargement and traction bronchiectasis.
- Changes found on the CT were more likely to be bilateral, peripherally distributed, and involving the lower lobes.³

DISCUSSION

From this review of the concerned literature, authors elicited several important indicators that may lead to rapid, accurate and early diagnosis of high-risk patients¹. Authors have also attempted to provide insights into how the condition progresses and affects the various organ systems throughout its course². It also describes scenarios to ensure efficient resource allocation, such that patients that are at a higher risk for poorer outcomes may be identified early in the treatment process. This will ensure that their treatment be managed efficiently and progress be made accordingly.

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