How COVID-19 kills

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COVID-19 Actuaries Response Group – Learn. Share. Educate. Influence.

Summary

This bulletin summarises how COVID-19 kills. COVID-19 damages the lungs, causing death. The joint culprits are the virus and an over-reacting immune system.

This is what we see

More than 190k people have died of COVID-19 worldwide to date. In EU/EEC countries about 30% of infected people require hospitalisation and 4% go into intensive care units (ICU)[1]. Of those hospitalised, 12% died.

Those that require hospitalisation and ICU often present with low blood-oxygen levels, suggesting the disease interrupts with oxygen transfer from the air into the blood stream. Normal blood-oxygen levels are above 94% (SpO_2), if it drops below 90% the brain may not get sufficient oxygen and below 80% vital organs may suffer damage[14]. COVID-19 patients with blood-oxygen below 92% are considered seriously ill and would be treated in the hospital or ICU.

UK's ICU data of 17 April show that COVID-19 can cause lung problems, without the presence of other diseases or frailty[2] (the 'control group' below are otherwise equivalent non-COVID-19 viral pneumonia patients of the last two years):

- Higher percentage of COVID-19 patients, 69%, need mechanical ventilation within the first 24 hours in ICU, compared with 43% control;
- Higher percentage of COVID-19 ICU patients do <u>not</u> have a severe co-morbidity, 93% compared with 76% control. 93% of COVID-19 patients do not need assistance for daily living, compared with 74% control;
- Fatality in ICU for COVID-19 is much higher than their control counterparts in all subgroups observed. The reason for this is being debated. Possible reasons are that antivirals are available for influenza but not coronavirus, and that COVID-19 may cause lung damage earlier[15].

Autopsies of patients who unfortunately died of COVID-19 show[3,4]:

- Damage to the tiny air sacs, alveoli, whose function is to exchange oxygen and carbon dioxide to and from the blood stream. This is supported by X-rays showing ground-glass opacity, indicating acute respiratory distress syndrome.
- Inflammation in the lung, with the presence of immune cells lymphocytes. The over-reaction of the immune system, the 'cytokine storm', could cause collateral damage to the cells in the lung. As puss and fluid build up, the function of the lung is compromised and the patient cannot breathe normally.
- Mucous in the lung.
- Bleeding (haemorrhage) and blood clots in the lung. This signifies damage in the blood vessels.
- Infection in the heart is not ruled out.

This is what's happening

For coronavirus to replicate by hijacking the cell, the virus needs to attach to the surface of the cell and enter it. The coronavirus attaches to a protein called ACE2 on the cell surface and requires some other proteins, one of them named TMPRSS2, to enter the cell. Laboratory scientists have recently reported that ACE2 and TMPRSS2 are associated with respiratory tract cells lined with hair-like projections to sweep mucus and bacteria out of the lung[5]. This would explain why COVID-19 affects the lung.

ACE2 and TMPRSS2 also appear on the cells of the heart, immune system, blood vessels, kidney, brain and intestines[6]. The functions of these organs and systems have been shown to be disrupted, to various degrees, by COVID-19. ACE2 increases with age and is 50% higher in men than women. This may explain why older people, especially men, are more affected by COVID-19.

The immune system is expected to play a role in damaging the lung as shown in autopsy[6]. Heidi Ledford explained further in Nature,

> *"Some of the earliest analyses of coronavirus patients in China suggested that it might not be only the virus that ravages the lungs and kills; rather, an overactive immune response might also make people severely ill or cause death. Some people who were critically ill with COVID-19 had high blood levels of proteins called cytokines, some of which can ramp up immune responses. These include a small but potent signalling protein called interleukin-6 (IL-6). IL-6 is a call-to-arms for some components of the immune system, including cells called macrophages. Macrophages fuel inflammation and can damage normal lung cells as well. The release of those cytokines, known as a cytokine storm, can also occur with other viruses, such as HIV."*[7]

The cytokine storm could also be responsible for harming other organs including the heart, liver, kidney and others.

How do other underlying conditions contribute to COVID-19 deaths?

People who are at higher risks of more severe symptoms are those who are older (over 50s), men, with underlying conditions including hypertension, obesity, smoking, respiratory diseases, cardiovascular diseases and others. They play different roles in causing deaths.

Direct role of other conditions

Chronic respiratory diseases and non-COVID-19 lung infection would directly add to the distress caused by COVID-19 in the lung. Diseased organs, such as the heart and kidney, will be more susceptible to damage due to oxygen deprivation from lung damage and cytokine storm from COVID-19, eventually leading to death.

This is consistent with the top five pre-existing conditions of people who died with COVID-19 in England & Wales (table below). The proportions of pre-existing lung-related diseases, chronic lower respiratory and influenza & pneumonia, of people who died with COVID-19 are relatively high when compared with observed in the population in 2018[9,10]. COVID-19 would have added further stress to diseased lungs.

For men, the proportion of COVID-19 deaths with ischaemic heart disease is higher than that in the population (see table below). Many COVID-19 patients die from cardiac arrest potentially triggered by oxygen deprivation or cytokine storm. But we still don't know if the problems are direct consequences of the virus infecting the heart[6].

Diseases	Men		Women	
	COVID-19 Age 70+ (85% age 80+)	Population 2018 Age 80+	COVID-19 Age 70+ (89% age 80+)	Population 2018 Age 80+
Chronic lower respiratory	12%	6%	14%	Under 5%
Influenza & pneumonia	11%	7%	11%	7%
Ischaemic heart	19%	12%	8%	8%
Dementia and Alzheimer	14%	15%	20%	24%
No pre-existing	9%	-	8%	-

Own calculations from ONS data [9,10]

The ability of COVID-19 to kill, with or without pre-existing diseases, lends support to debunk the preconception that people who die in this COVID-19 epidemic are primarily those 'at death's door'.

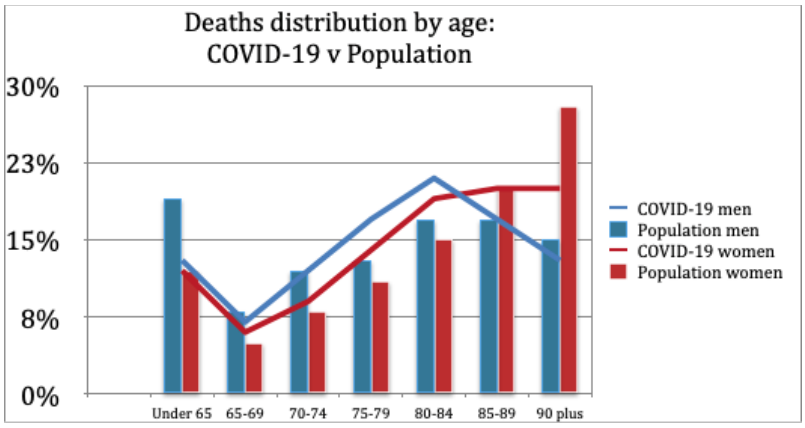
However, more research is needed to understand how the virus harms the body, including:

- The virus could theoretically attach to many organs and systems with ACE2 and other proteins. How does it affect them, leading to death?
- How does the cytokine storm affect the lung and other organs, leading to death?
- What have we missed in identifying how COVID-19 kills? For example, blood clots and damage in the blood vessels are increasingly suspected to play a larger part in harming the function of the lung and heart.[13]
- How do pre-existing conditions interact with COVID-19, leading to death? For example, diabetes has been suggested to present favourable conditions for viral infection and to impede part of the immune system. [14]

Indirect role of other conditions

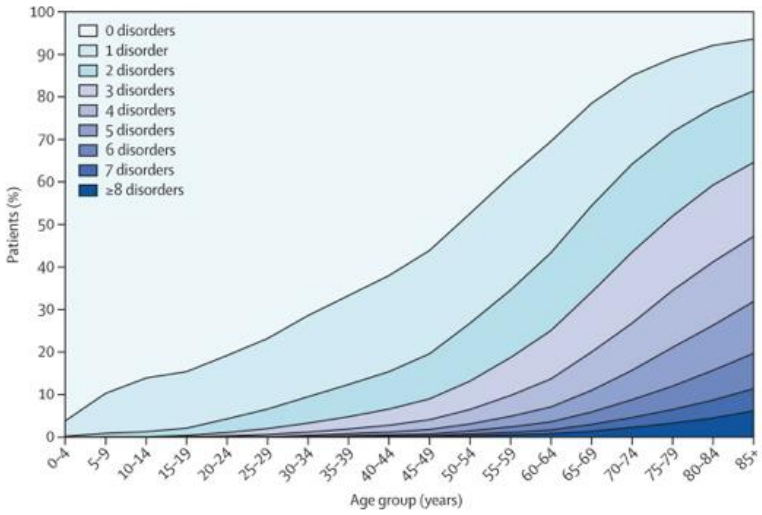
Many underlying conditions are proxies for age, rather than acting directly. Immunity declines with age, increasing the risk of inefficient response, lack of co-ordination and prolonged cytokines storms against infection[11, 12]. This is consistent with the observation in England & Wales that 4 in 10K people died with COVID-19 at age 55-59, rising to 76 in 10k at age 85-89, an increase of 19-fold, in March 2020 [10].

The 'shape' of the age distribution of deaths are similar between COVID-19 and the population. This is consistent with hypotheses that age drives COVID-19 deaths through weakened immunity and population deaths through chronic conditions related to damages caused by ageing processes. The proportions of COVID-19 deaths among men age 75-84, women 65-84, are higher than that of the population (Figure below). More work is needed to confirm if this is statistically significant and related to the cytokine storm being more prevalent in these age groups.



COVID-19 data in March 2020 and population in 2018, in England & Wales, from the ONS [9, 10].

Research shows that the prevalence of underlying conditions rises with age, regardless of COVID-19. For example, about 30% of people age 30-34 have at least one chronic disorder increasing to 90% for age 75-79 in Scotland[8] (see figure below). Although COVID-19 patients tend to have underlying conditions, it is unclear how, or if, they contribute to deaths. More work is required to better understand how interactions of various underlying conditions affect the progression of COVID-19.



Snapshot of Barnett et al. (2020), The Lancet.

Comments

Emerging evidence shows that COVID-19 can damage the lung, leading to low blood-oxygen levels and death. The joint-culprits are the virus and an over-reacting immune system. The virus infects primarily the lung and potentially other organs including the heart and kidney. Our own immune system may over-react, leading to cytokine storm that damages these organs. This damage, combined with oxygen deprivation, kills.

References

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