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Commentary

Age, frailty and diabetes – triple jeopardy for vulnerability to COVID-19 infection

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In December 2019, a pneumonia like illness was first reported in Wuhan-China caused by a new coronavirus named corona virus disease –2019 (COVID-19) which then spread to cause a global pandemic. The epidemiology of COVID-19 incidence, severity of illness and mortality seem to be shifted towards older people particularly those with multiple comorbidities such as diabetes, hypertension, and cardiovascular disease [1]. However, frailty, which affects more than one in five older people with type 2 diabetes, worsens prognosis in severe acute illness and is a better predictor of ICU (intensive care unit) outcomes.

In an epidemiological characterization and analysis of 72,314 cases of COVID-19 pneumonia reported in China, the majority of cases (89.8%) were between the age of 30 to 79 years old and the proportion of cases in the elderly (> 60 years) was 44.1%. The overall case mortality rate was 2.3% but this rate increased proportionally with age reaching 8% in those aged 70–79 years and 14.8% in those ≥80 years old [2]. Older age was also identified as a risk factor for mortality from COVID-19 pneumonia in a Chinese retrospective, multicentre cohort study {odds ratio (OR) 1.10, 95% confidence interval (CI) 1.03 to1.17, $p = 0{\cdot}004$) [3]. In another study old age was a significant risk factor for the development of acute respiratory distress syndrome (ARDS) and the progression from ARDS to death {hazard ratio (HR) 3.26, 95% CI 2.08 to 5.11; and 6.17, 3.26 to 11.67, respectively) [4]. Age-related impairment in the immune system function may also be a factor. The ageing immune system is characterized by a low grade and chronic systemic inflammatory state or "InflammAgeing" marked by elevated inflammatory markers such as IL- 6 and C-reactive protein and is associated with an increased susceptibility to infection.

Globally, it is estimated that 19.3% of people aged 65–99 years (135.6 million, 95% CI: 107.6–170.6 million) live with diabetes [5], and diabetes, and is known to be associated with an increased risk of corona viral pneumonia. In a meta-analysis of 8 Chinese studies to assess the prevalence of comorbidities in 46,248 infected patients with COVID-19, median age 46.0 years (51.6%) men, diabetes mellitus was the second most prevalent comorbidity (8%) after hypertension (17%) and higher than cardiovascular (5%) and respiratory diseases (2%) [2]. However, diabetes appears to be mostly associated with severe cases of COVID-19 infection. Patients infected with COVID-19 who required intensive care (IC) treatment were more likely to have diabetes (22.2% v 5.9%) compared to those who did not require IC admission [6]. Presence of diabetes increased mortality from COVID-19 compared with persons without comorbidities (7.3% V 0.9%) [2]. Diabetes may increase the risk of viral infection because of impaired innate immunity due to impaired macrophage and lymphocytes function which also increases the speed of progression to septic shock and multiple organ failure leading to poor outcomes. Higher sequential organ failure assessment score was identified as a risk factor for mortality in COVID-19 patients (OR 5.65, 95% CI 2.61 to 12.23, $p<0{\cdot}0001$) [3]. Since the COVID-19 virus gains entry to pulmonary cells through binding to membrane ACE2 receptors which are distributed widely in lung, intestine, kidney, and blood vessels, it is possible that increased ACE2 receptor expression in both type 1 and type 2 diabetes (e.g. by angiotensin receptor blockers (ARBs), angiotensin converting enzyme (ACE) inhibitors and non-steroidal anti-inflammatory drugs) may increase COVID-19 infectivity and illness severity.

Old age and diabetes are associated with an increased risk of frailty [7]. Frailty is a syndrome that is characterised by multisystem dysregulation that leads to reduced physiologic reserve and increased risk of adverse health outcomes. Dysregulation in the innate and adaptive immunity also leads to chronic inflammation, with increase in inflammatory markers, and increased susceptibility to sever infections. Frailty may be linked to infectious disease through common pathways that reduce immunity. Increased inflammatory markers have been shown in patients with viral pneumonia. Although frailty was not formally assessed in the COVID-19 infection trials, old age associated with comorbidities including diabetes were associated with an increased risk of infection and worse outcome. Inflammatory markers such as IL-6 were most elevated in severe cases COVID-19 infection which may be suggest increased prevalence of frailty in this cohort [3]. Frailty has also been shown to be associated with poor post-vaccination immune response and increased rates of influenza like illness and laboratory-confirmed influenza infection [8]. In a prospective cohort study in a tertiary hospital investigating older

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patients (aged ≥65 years) admitted with community acquired pneumonia, nursing home residency (a proxy for frailty) was an independent predictor of viral pneumonia {relative risk (RR) 3.06, $P = 0.01$) which highlights the role of frailty in institutionalised populations for the increased risk of viral illness [9].

Key steps to maintain health in this highly vulnerable group of people include daily exercise (boosts immunity, improves glycaemic control, reduces the risk of infection), keep well hydrated, review use of SGLT2 inhibitors if unwell (risk of diabetic ketoacidosis), and maintain access to medical advice through telemedicine or telephone/video conversation. Whilst frailty should join advanced age as a resource determinant in planning ITU services to tackle Covid-19, other factors apart from frailty measures should be used to determine access to critical care organ support at admission to hospital [10].

Frailty should be considered in risk assessment models in future clinical trials to ensure developing vaccines that have a favourable immune response in frail individuals. Viral entry into the cell membrane through the ACE2 receptors also needs further study to determine whether ACE2 polymorphisms may increase individual susceptibility to Covid-19.

1. Useful links

https://www.who.int/emergencies/diseases/novel-coronavirus-2019

https://www.gov.uk/government/topical-events/coronavirus-covid-19-uk-government-response

https://www.nice.org.uk/coronavirus

https://www.diabetes.org.uk/about_us/news/coronavirus

Declaration of Competing Interests

The authors declare no competing interests.

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