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Comorbidities, multimorbidity and COVID-19

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Abstract

The influence of comorbidities on COVID-19 outcomes has been recognized since the earliest days of the pandemic. But establishing causality and determining underlying mechanisms and clinical implications has been challenging — due to the multitude of confounding factors and patient variability. Several distinct pathological mechanisms, not active in every patient, determine health outcomes in the three different phases of Covid-19 – from the initial viral replication phase to inflammatory lung injury and post-acute sequelae. Specific comorbidities (and overall multimorbidity) can either exacerbate these pathological mechanisms or reduce the patient's tolerance to organ injury. In this review, we consider the impact of specific comorbidities, and overall multimorbidity, on the three mechanistically-distinct phases of Covid-19, and we discuss the utility of host genetics as a route to causal inference by eliminating many sources of confounding. Continued research into the mechanisms of disease state interactions will be crucial to inform stratification of therapeutic approaches and improve outcomes for patients.

Introduction

Understanding the impact of comorbidity in Covid-19 has two broad purposes — it enables prognostication and prioritisation for interventions such as preventive measures, vaccination and early treatment. These principles are reflected in public health guidance prioritizing some groups for vaccination, and clinical guidance to use anti-virals to prevent hospitalization in people with specific comorbidities. Some risk factors reveal mechanisms that either exacerbate the underlying disease processes, or reduce the ability of a patient to cope with the injurious consequences of these processes.

The importance of comorbidity in modifying severity and outcomes in COVID-19 was recognized in the earliest scientific reports.[1,2] Here, we use the term comorbidity to refer to any long-term health condition that coexists in an individual with a specific condition of interest, in this case COVID-19.[3] This is distinct from multimorbidity, which describes the presence of two or more long-term health conditions in an individual without reference to COVID-19 - and is in itself a major and growing public health challenge.[4] Modelling studies estimated that 1.7 billion people globally (22% of the population) have at least one co-morbidity associated with an increased risk of developing severe COVID-19.[5]

The most direct evidence relating to the clinical impact of any comorbidity comes from epidemiological associations with key outcome measures. In acute COVID-19, the most widely-used outcomes describe disease severity with pragmatic measures including hospitalization, requirement for oxygen treatment or organ support and mortality.[6] Interpretation of associations between various comorbidities and disease severity outcomes requires consideration of the distinct biological events, social factors and clinical decisions that lead to these outcomes. Although we have convincing evidence that host features (e.g. age, sex and genetics) are primary determinants of disease progression,[7,8] it is important to note that comorbidities can also affect risk of exposure: both increasing risk (for example, in outbreaks in care homes) and decreasing it (for example, through shielding behaviours). The clinical decisions to admit a patient to hospital or to initiate organ support are also strongly influenced in complex ways by the presence of comorbidities, multimorbidity and frailty, and even an objective outcome such as mortality can be difficult to interpret because different sequences of biological events can lead to death.

Like many other potentially life-threatening infectious diseases, the spectrum of disease severity

resulting from SARS-CoV-2 infection is wide, with asymptomatic infection the most likely outcome and life-threatening disease extremely uncommon. Importantly, Covid-19 has three distinct phases (**Box 1**) which we categorise as acute viral illness, immune-mediated inflammatory lung injury, and post-acute sequelae of COVID-19 (PASC).[9] Each of these phases has divergent responses to therapy and different underlying biological mechanisms which, to some extent, vary across different groups of patients.

In this review, we first discuss the challenges associated with comorbidity-outcome associations, including the potential biases and confounding factors that can influence their interpretation. Next, we consider the impact of specific comorbidities and overall multimorbidity on three mechanistically-distinct phases of Covid-19. In each phase, where evidence exists, we consider the implications of associations with comorbid illness in driving the underlying pathophysiological mechanisms, or in reducing a patient's tolerance of the consequences of those mechanisms. For example, some comorbidities worsen immune-mediated lung injury by reducing viral clearance or exacerbating inflammation, whereas other comorbidities reduce lung function at baseline, predisposing to respiratory failure at a level of lung injury that would normally be well-tolerated. Synthesising epidemiological and host genetic signals with current understanding of the underlying mechanisms of disease, we draw some tentative conclusions about implications of comorbidities in Covid-19, and how future work can maximise the value of our existing knowledge base.

Navigating causality and confounders

Findings from large, observational studies have been used as the starting point to inform hypotheses to explore the biological mechanisms through which comorbidities predispose individuals to severe COVID-19. However, caution needs to be exercised before inferring causality from these associations. Spurious or distorted associations can arise for several reasons relating to study design and sampling, and interpreting putative causal relationships between specific comorbidities and acute COVID-19 is difficult due to complex relationships with outcomes.

Associations reported between comorbidities and outcomes in studies of hospitalized populations with COVID-19 could be biased due to the criteria for entry into the study (that is, requirement for hospitalization) being causally associated with both the comorbidity (collider bias) and the outcome.[10] Studies undertaken in populations not restricted to hospitalized individuals are less likely to report associations affected by this bias. However, comorbidity-outcome associations can be distorted if sampling does not require hospitalization, including in cohorts sampled from general populations, because the risk of developing the outcome (usually severe COVID-19 disease) is a combination of the probabilities of contracting the virus, seeking testing, and developing severe disease. Studies that use a positive PCR test as part of the case definition usually rely on non-random testing, which could be biased by associations between testing patterns and features related to comorbidity status and/or severity (e.g. hospitalization or severe symptoms).

Similarly, the likelihood of being exposed to the virus might differ by comorbidity status, particularly if non-pharmacological interventions, such as shielding or compliance with mask wearing, are more common in those with comorbidities. Those with comorbidities might also be more cautious about social interactions, even when public health authorities no longer advise non-pharmacological measures.[11]

Even when a comorbidity causally influences outcomes, the underpinning mechanisms might not be specific to COVID-19. Comorbidities can predispose an individual to hospitalization and even intensive care unit (ICU) admission as a result of almost any acute illness, a nonspecific concept that is widely-understood among clinicians, but often impossible to quantify in biological terms. Specific examples include lung conditions such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, which can be measured by objective reduction in lung function tests, and chronic kidney disease, which is quantified by reductions in glomerular filtration rate. These measurable reductions in the functional capacity of specific organs magnify the proportional impact of a new insult - there is less function to lose before the organ fails to meet the minimum requirements for survival. Frailty, malnourishment, and chronic illness without organ dysfunction can impair

an individual's capacity to tolerate even a relatively minor physiological stressor, resulting in an increased likelihood of hospitalization and or the need for organ support.

Caution is also needed when severity is defined by health service use or intervention (that is, hospitalization, critical care admission or respiratory support), as the presence of comorbidity might influence clinical decision making, either lowering or increasing the threshold for hospitalization or provision of organ support. This is not specific to clinical management of COVID-19: in a multicentre, Europe-wide study of ICU patients with acute respiratory distress syndrome, patients with a comorbidity were less likely to receive invasive mechanical ventilation and other interventions for severe hypoxaemia than those without.[12] It is possible that the extreme capacity strain in many areas during the peaks of the COVID-19 pandemic may have augmented this effect.

When the effectiveness of an intervention is not reliant on mechanisms specific to the comorbidity–outcome relationship, comorbidities can simply act as prognostic markers of poor outcomes. Because the best evidence suggests that common comorbidities do not have markedly differing effects on risk of death,[13] the widely-used and validated 4C score for COVID-19 mortality risk, an early output from the ISARIC4C study,[8] does not separate individual comorbidities, using only the total number of comorbid illnesses present (**Figure 1**). This pattern is consistent with other studies on the impact of comorbidity on risk of acute disease. However, some specific comorbidities merit consideration in COVID-19 due to their potential mechanistic implications (discussed in sections below).

One highly effective method to test causal mechanistic hypotheses is Mendelian randomization (**Box 2**), which uses the random genetic variation across the population to draw an inference about the causal link between one biological observation and another. Mendelian randomization has some general limitations[14] — most importantly, the assumption that the causal pathway between a gene and a disease outcome is mediated through a single route. This limitation is particularly important in the context of comorbidities and COVID severity, since the assumption of a single causal pathway is less plausible, and is untestable. Nevertheless, this approach has proved a valuable tool in the complex task of differentiating association from causality, and formed the bases of several key studies discussed in the sections below.

Impact of comorbidities during each phase of COVID-19

COVID-19 was initially described as a biphasic illness,[15] by a Chinese group using the ISARIC Clinical Characterisation Protocol[16] — and this quickly became familiar to clinicians worldwide. It was noted that death could occur by two different routes, as both the initial viral illness (associated with high viral replication in the upper respiratory tract) and the later inflammatory lung injury phase, can cause life-threatening disease.[17–19]

The strongest evidence for mechanistic differences between the acute viral illness and the inflammatory lung injury phases of Covid-19 comes from the RECOVERY trial results for dexamethasone.[20] This study was remarkable for its speed and the scale of its impact, but also because it is a rare example of a major change in clinical practice due to a subgroup analysis in a single trial. The results showed net benefit overall, but a prespecified subgroup analysis indicated a greater reduction in mortality among patients requiring invasive ventilation, and a trend towards harm among patients not requiring oxygen, at the time of randomization. Just as the impact of this treatment differs between hypoxic and nonhypoxic COVID-19, the impact of some comorbidities is also likely to differ between the two disease phases.

Among patients who require prolonged invasive ventilation, there is an accumulating risk over time of complications associated with organ support and prolonged critical illness (**Figure 2**). These include critical illness neuropathy and myopathy,[21] secondary infections including ventilator associated pneumonia, and delirium. These problems are not unique to patients with Covid-19 but are an important mechanism by which comorbid illnesses can significantly increase mortality by reducing tolerance of injury.

Although most people infected with SARS-CoV-2 fully recover, a significant minority of survivors develop persisting symptoms – either due to the virus itself, a non-resolving host inflammatory response, or non-specific effects of critical illness – leading to the concept of COVID-19 as a triphasic illness.

The upcoming sections discuss the existing evidence linking comorbidities to COVID-19 outcomes during each of these distinct phases of COVID-19.

Acute viral illness

In this section we discuss comorbid illnesses likely to have their greatest impact during the initial phase of disease, when viral replication is greatest. We do not suggest that this phase and subsequent phases are independent - indeed, host genetic evidence suggests that impaired control of viral replication, for example due to defective Type I interferon signalling, predisposes to lung inflammation.[22] There is a growing body of evidence, from observational studies and clinical trials of antivirals, suggesting that lung inflammation is to some extent proportional to, and primed by, viral load — and is not an idiosyncratic immune response.[23] Hence, the disease associations discussed here are also likely to predispose to inflammatory lung injury.

In order to synthesise a mechanistic understanding of pathogenesis with the observed associations with clinical outcomes, we draw a distinction between comorbidities expected to affect either resistance to viral infection, or tolerance of the consequences. We use the term resistance to describe the ability of the host to control pathogen replication, whereas the term 'tolerance' in the context of this review describes the ability of a patient to cope with a given degree of injury (whether pathogen- or host-mediated).

Studies restricted to patients hospitalized with COVID-19 demonstrate a substantially higher prevalence of comorbidity than in the general population. In the ISARIC4C study, which recruited patients hospitalized with COVID-19 in the UK using a globally-harmonised protocol,[16] more than three-quarters of patients had at least one comorbidity, and patients with cardiac disease, pulmonary disease, chronic kidney disease, obesity, cancer, chronic neurological disorders, dementia and liver disease had an increased risk of in-hospital mortality.[2] Similar findings were reported for a more limited set of comorbidities in early reports from mainland China, albeit limited by sample size.[1] The need to rapidly mobilize data collection on affected patients necessitated limitation of these early studies to hospitalized populations, comprising a mixture of patients requiring hospital care due to acute viral illness, and inflammatory lung disease. In a wider cohort study using primary care data from 40% of the English population,[24] 15 comorbidity groupings were evaluated together with body-mass index (BMI). The commonest comorbidities were hypertension (34.3%) followed by asthma (15.9%) and diabetes (9.9%). In age- and sex-adjusted regression models, all comorbidity groups were associated with increased risk of death from COVID-19, with the greatest risk found in organ transplant recipients (hazard ratio (HR) 6.00 (95% CI 4.73–7.61)) and in those with chronic kidney disease (HR 3.48 (3.23–3.75)). For most comorbidity groupings, the magnitude of associations was greater in analyses restricted to the earlier pandemic period, shortly after social distancing and shielding policies were introduced. This highlights the need to interpret associations in the context of wider societal determinants that modify exposure to the virus.[11]

Specific immune effector mechanisms required for effective resistance vary by pathogen. For example, people with neutropenia are at specific risk of invasive infection with gram-negative bacilli compared to people with normal neutrophil function[25]. In contrast, since Staphylococcus aureus persists within neutrophils as a mechanism to disseminate to distant sites via the bloodstream, S. aureus disease is under-represented in people with neutropenia.[26] 'Immunosuppression' as a broad term is therefore unhelpful in understanding pathogenesis of infectious agents, but specific examples contribute to the identification of key effectors of resistance. SARS-CoV-2 replication occurs in the upper respiratory tract, where expression of ACE2 (the receptor that mediates SARS-CoV-2 viral entry) is highest, and viral load at this site is positively correlated with disease severity.[27–29]

Although organ transplant recipients are one of the groups at greatest risk of mortality from Covid-

19,[24] an analysis of a large US COVID-19 database (n=222,575) found that immunosuppressive therapy before hospitalization (for any reason, including transplant) was not associated with in-hospital mortality.[30] However, when individual drug classes were considered, increased mortality was seen specifically for the B-cell depleting anti-CD20 monoclonal antibody rituximab. In 422 people with COVID-19 who had recently received treatment with anti-CD20 therapy (330 of whom received rituximab) for comorbid auto-inflammatory diseases, in-hospital mortality was associated with more recent (<6 months) receipt of the drug and 61% of infected people had received their most recent dose within 3 months.[31] In this study, anti-CD20 treatment was also associated with prolonged upper respiratory tract viral shedding and relapses. Seroconversion was associated with more distant receipt of anti-CD20 therapy and lower likelihood of virologic recurrence.

The consequences of infection with human immunodeficiency virus (HIV) identify another component of the adaptive immune system that contributes to resistance to SARS-CoV-2. People living with HIV who are hospitalized due to COVID-19 are younger and have higher in-hospital mortality than those without HIV.[32] In hospitalized people with HIV and COVID-19, a CD4 T-cell count of less than 350 cells/μL was independently associated with severe disease.[33] In a cohort of people living with HIV who were established on antiretroviral therapy for over 2 years, with an undetectable viral load and CD4 T-cell counts of 133–1360 cells/μL, a positive relationship was found between the CD4:CD8 ratio and extent of T-cell activation against SARS-CoV-2.[34] Therefore, despite virologic suppression and apparent immune reconstitution, subtle defects that compromise T-cell responses are likely to remain in people living with HIV. The implications of B-cell depleting immunosuppressive therapies and HIV associated T-cell impairment on Covid-19 pathogenesis identifies these immune responses as crucial for COVID-19 resistance, consistent with observations from human immunology studies of respiratory syncytial virus.[35]

Other comorbidities associated with altered immune function could provide further mechanistic information about resistance to SARS-CoV-2, but require further investigation. Cytomegalovirus (CMV) is a ubiquitous herpesvirus that latently infects most human beings. Reactivation can occur in the context of lymphoid immunosuppression, including advanced HIV infection, critical illness or immunosuppressive therapy. Although reactivation can lead to end organ disease (for example, pneumonitis), latent infection is also associated with immunological perturbation and potentially immunosenescence.[36] As expected, CMV reactivation has been documented in severe COVID-19.[37,38] However, specific sampling of the respiratory tract indicated that latent CMV infection is associated with both increased likelihood of COVID-19 and increased disease severity, even in the absence of virologically-confirmed CMV reactivation.[39] This association was replicated in a second cohort, where an adjusted analysis demonstrated that the risk was independent of age and other comorbidities, and that CMV seropositivity was most strongly associated with severe disease in people aged under 60 years.[40] T-cell alterations – specifically activation of effector memory T cells expressing CD45RA – in CMV-seropositive people with COVID-19 are similar to those in seropositive people without COVID-19.[39] Any immunological effects of latent CMV on COVID-19 pathogenesis are therefore likely to be distinct from classical T-cell consequences.

In COVID-19, recent work suggests that variants affecting the key viral entry mechanisms for SARS-CoV2 in human cells (ACE2 and TMPRSS2 proteins) alter the probability of severe disease.[41] However, ACE2 is also involved in blood pressure homeostasis and ACE inhibitors, used as a first-line approach to managing hypertension, are associated with increased *ACE2* expression in some organs.[42] Multiple studies early in the pandemic reported increased risk of mortality in people with hypertension, leading to the biologically plausible hypothesis that this was mediated via increased expression of the viral receptor ACE2 (although this has now been disproven[43]). The epidemiologic association between hypertension and COVID-19 has not been confirmed in larger more robust studies (reviewed in[44]). Furthermore, *ACE2* expression in alveolar pneumocytes is actually infrequent, and virus arrives in the distal lung after uptake by migrating macrophages.[28] These macrophages take up virus particles by endocytosis and no productive replication occurs, but this is associated with macrophage activation, engagement of a pro-inflammatory programme, and associated alveolar injury.[45] Therefore, although superficially plausible, there is no definitive link between *ACE2* expression and lung pathology in COVID-19. The putative association with hypertension has not been consistently reproduced and ACE2 inhibition does not upregulate ACE2

protein expression by airway epithelial cells. *ACE2* expression is, however, up-regulated in people with chronic obstructive pulmonary disease,[46] and this has been confirmed at the protein level in respiratory samples.[47] Nevertheless, in our view, a reduced threshold for respiratory failure is more likely to underlie the association of COPD, rather than *ACE2* expression, with mortality in COVID-19. More broadly, this highlights the implications of frailty and multi-morbidity on COVID-19 pathogenesis.

The significant association, in multiple studies, of a very broad range of comorbidities with hospitalisation and death, is consistent across not only studies of COVID-19, but also a range of other respiratory and systemic illnesses. This, together with the strong and consistent signal for multimorbidity as the strongest risk factor, suggests that the impact of these comorbidities is not specific to COVID-19, or even to respiratory disease. Patients with severe underlying chronic disease often maintain a precarious level of function, in which an acute pyrexial illness may precipitate decompensation of the underlying disease. This is consistent with an observational study of pre-morbid ECOG (Eastern Cooperative Oncology Group) performance status on outcomes of acute COVID-19. After correcting for relevant physiologic variables, performance status (which was positively correlated with the number of comorbidities) remained independently associated with in-patient mortality with an effect size greater than than age. Similar findings have been reported using the Clinical Frailty Score.[48] This leads us to conclude that the major impact of most comorbidities in the acute viral illness phase is a generic consequence of frailty and reduced physiological reserve.
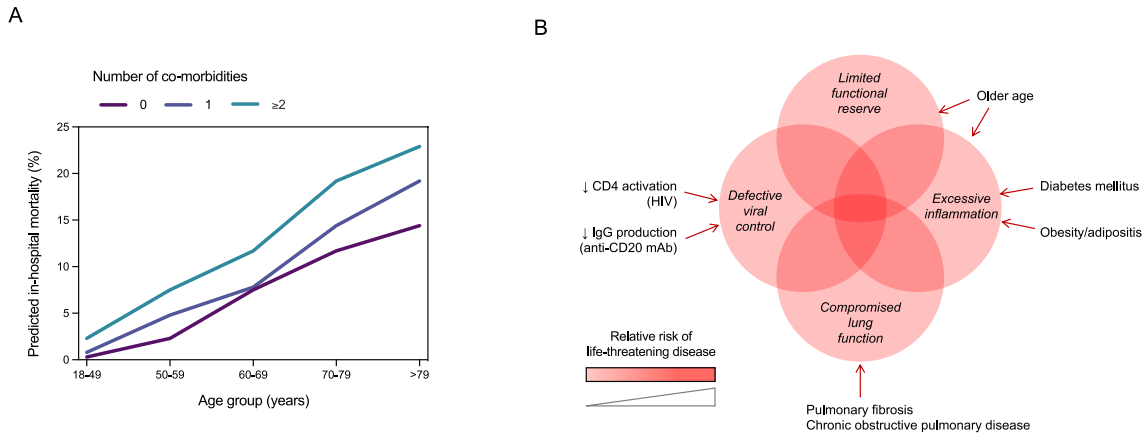

Figure 1: (A) To illustrate the impact of multimorbidity, the ISARIC 4C Mortality score was used to predict in-hospital mortality for a hypothetical male patient in different age groups with a different number of co-morbidities, assuming other variables used in the score remained the same (respiratory rate <20 breaths/minute; peripheral oxygen saturations >91%; Glasgow Coma Scale score 15; urea <7mmol/L; C-reactive protein <50mg/L). The graph illustrates the increasing risk of mortality with increasing age and increasing number of comorbidities, and that comorbidity count has an additive effect to age. (B) Additive effects (indicated by color shading) exerted by co-morbidities (multi-morbidity), contributing to disease severity through different potential mechanisms.

Inflammatory lung injury

The general effects of comorbidities and/or frailty are also expected to reduce tolerance of hypoxaemic respiratory failure, which is the clinical consequence of inflammatory lung injury. Some comorbid illnesses are also thought to have specific effects that either drive the underlying disease process (e.g. adipositis in obesity), or specifically reduce tolerance of respiratory failure (e.g. chronic respiratory disease, neuromuscular disease; Figure 1B).

For comorbidities that have been studied intensively using human genetics, Mendelian randomisation offers an opportunity to test the hypothesis that each comorbidity directly causes severe or fatal outcomes in COVID-19. One such comorbidity — obesity — has been consistently found to

be associated with critical COVID-19 in Mendelian randomization studies.[49] Although robust as a tool to rapidly identify variants associated with COVID-19, the reliance of this study on opportunistic population control groups could inflate the effect of genes associated with obesity, since population genetic studies (such as UK Biobank) are enriched for patients with lower BMI.[50] This in unlikely to affect the primary, genome-wide significant findings of the study because they are robust to sensitivity analyses controlling stringently for BMI. However, Mendelian randomisation in this context relies on the signals from weaker genetic associations which have not been confirmed in the same way. Most of these limitations apply equally to the many other comorbidities associated with poor outcomes in COVID-19, so it is of interest that the effect of obesity and adiposity is both consistent[49] and that similar effects are not observed for other common and related conditions.[49] Since the genetic signals underlying this observation arise primarily from a study among critically ill patients only,[51] we consider it likely that this effect is be mediated through pneumonitis, rather than frailty. One plausible mechanism through which obesity might influence the development of pneumonitis is through low-grade systemic innate immune inflammation (adipositis), which might predispose the infected organ to innate immune injury when viral replication is not contained in the early phase of the illness (**Figure 1**, **Figure 2B**). We have previously proposed a similar mechanism in life-threatening influenza.[52]

Although not supported by a strong Mendelian randomisation signal, an association was identified early in the pandemic between diabetes and life-threatening disease in hospitalized people with COVID-19.[2] Due to shared risk factors, T2D often co-occurs with obesity and cardiovascular disease, and is more prevalent in older individuals. In an attempt to disentangle this, an analysis using data from a nationwide diabetes registry in Sweden and matched population controls found that T2D (n=385,021) remained an independent risk factor for both hospitalization and ICU admission in patients with COVID-19, after adjustment for age and comorbidities.[53] Although this study did not identify type 1 diabetes (T1D) itself as an independent risk factor (n=44,478 with T1D), poor glycaemic control in the context of T1D was associated with these outcomes. In the Swedish cohort, BMI was one of the strongest predictors of adverse outcomes in patients with T2D and COVID-19. Glycaemic control in T2D, assessed by glycated haemoglobin (HbA1c), is strongly associated with obesity.[54] In a US cohort of people with T2D and COVID-19, poor glycaemic control (determined by HbA1c levels) was associated with hospitalization, ICU admission and invasive mechanical ventilation or ECMO.[55] Given the relationship between T2D, glycaemic control and obesity, Mendelian randomization approaches have been applied to differentiate association from causation in COVID-19 severity. T2D itself has consistently not been found to be causally associated with adverse outcomes in COVID-19, in contrast to the closely related trait of obesity.[56,57]

People with diabetes have increased susceptibility to bacterial infections, especially skin and soft tissue infections and invasive infections involving Gram-negative bacteria. Hyperglycaemia can act directly as a pro-bacterial factor in the pathogenesis of skin and soft tissue infections[58], and a hyper-inflammatory response involving interleukin-1β (IL-1β) and IL-6 is implicated in severe Gram-negative infections.[59] Innate immune activation driven by IL-6 and associated with high levels of IL-1β is also associated with disease severity and implicated causally in fatal COVID-19.[20,60,61] Mechanistic studies have provided a link between diabetes and regulation of inflammation in COVID-19, especially involving monocytes/macrophages, which are likely to be important cell types driving immunopathology.[62,63] In COVID-19, T2D is associated with peripheral blood monocyte activation and transition to a CD14lo non-classical phenotype, along with increased expression of IL6 and CCL2, indicating a hyper-inflammatory phenotype.[64] Importantly, patients with T2D in this study also had a higher median BMI than the non-diabetic group (28 (interquartile range 24–32) versus 22 (21–22)), so these cellular phenotypes may be consequences of obesity, rather than T2D.

Although not strictly a comorbidity, the strong effect of coinfection with influenza on risk of invasive ventilation and death in the ISARIC4C study was not seen with coinfection with other respiratory viruses,[65] suggesting that common mechanisms underlying lung injury might be shared between COVID-19 and influenza. Importantly, the apparently strong impact of pregnancy on risk of severe influenza[52] is not apparent in COVID-19. Most strikingly of all, the risk of severe illness among

infants and young children is much higher in influenza[66] than in COVID-19.[67] However the effect of old age is very striking in both conditions - in COVID-19, risk of death is 11-fold greater among patients >80 years old than for those <50 years old.[2] A process with many similarities to adipositis, referred to as inflammaging – in which subclinical systemic inflammation exists, mediated in part by monocyte/macrophage activation by cell debris[68] – may predispose older patients to innate immune-mediated lung damage in COVID-19.

The interactions between inflammatory lung injury in Covid-19, adipositis, inflammaging, diabetes and co-infections provide some important clues about the underlying molecular mechanisms of organ injury in all of these conditions. Ongoing mechanistic work in each of these conditions will continue to deepen understanding of Covid-19, even in a future post-pandemic era when direct study of Covid-19 cases is no longer possible.
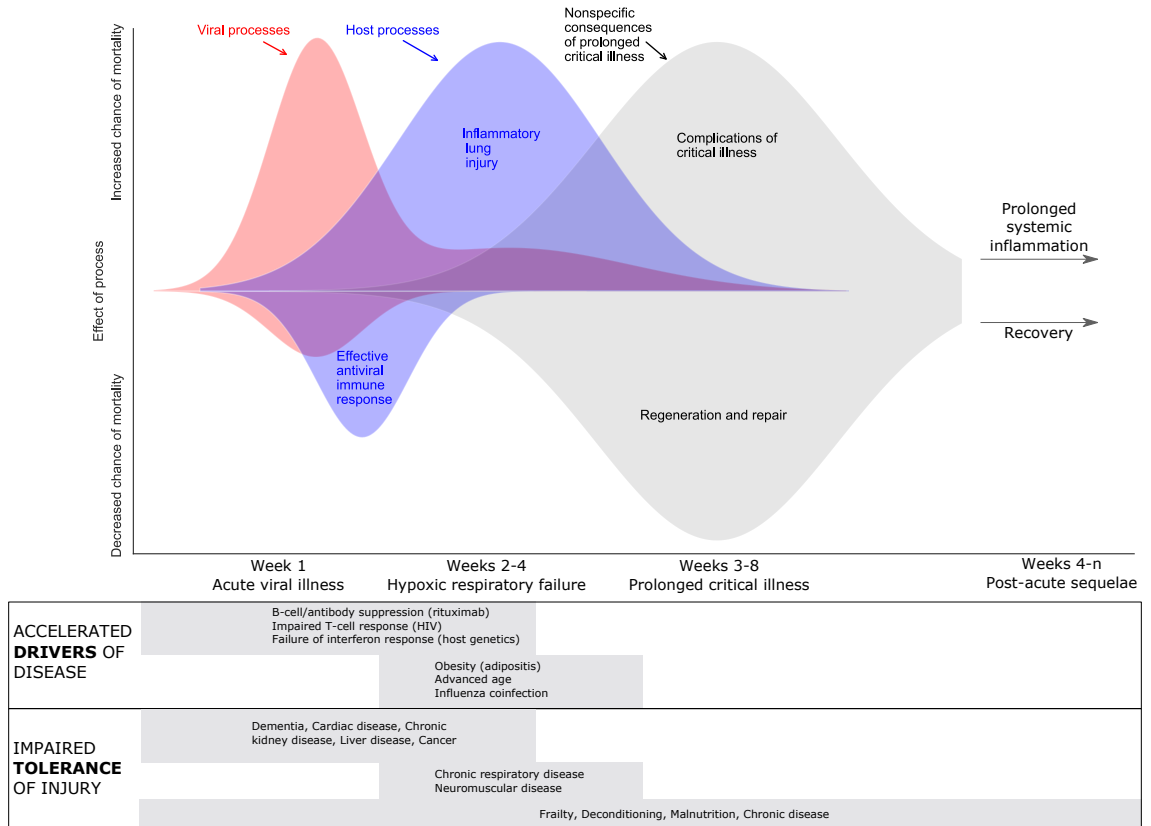

Figure 2: Figure 2: Phases of illness and likely impact of specific comorbidities. The progress of a range of biological processes are plotted over time, according to their hypothetical impact on the probability of survival. Those initiated by the virus (e.g. replication, production of virulence factors, inhibition of host interferon response) are shown in red; those initiated by the host (e.g. initial antibody response and cell-mediated immunity preventing viral replication, and later innate immune-mediated pulmonary inflammation) are shown in blue. The lower panels provide examples of comorbidities contributing to enhanced disease pathogenesis or impaired tolerance at each stage.

Recovery and post-acute COVID-19 sequelae

Those surviving critical illness from any cause, including non-infectious causes, have significant impairments in mental and physical health and health-related quality of life, as well as experiencing broader socioeconomic impacts and effects on family mental health, referred to as post-intensive care syndrome.[69–71] ICU survivors are also at increased risk of emergency rehospitalization for a sustained period after their index critical illness compared with non-critically ill hospitalized

patients.[72] Those with comorbidities before critical illness are less likely to return to baseline physical function,[73] and have more than double the risk of emergency rehospitalization compared with those without comorbidities.[74] For these reasons, careful analysis is required to identify whether post-acute COVID-19 sequelae are attributable and specific to SARS-CoV-2 infection, or whether they are driven by non-specific aspects of acute illness or hospitalization, or pre-existing comorbidity.

Separate post-intensive care syndrome, post-acute morbidity is recognized after several acute viral infections, including Dengue, SARS and influenza.[75–77] The World Health Organization (WHO) published a consensus case definition for post-acute sequelae of COVID-19 (PASC, also known as post COVID condition or long COVID) more than 18 months after the start of the pandemic: "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis."[9] The epidemiology of PASC has been comprehensively summarised elsewhere and is not discussed further here.[78,79] However, the specific influence of pre-existing comorbidities on PASC is becoming clearer as experience and research accrues; there is now clear evidence that people with pre-existing comorbidities are more likely to develop PASC than those without.[80]

One study found that prevalence of PASC ranged from 2.8% to 5.5% in people with pre-existing health conditions, compared with 1.8% in those with no health conditions.[81] In non-hospitalized individuals, multimorbidity is associated with increased risk of persisting symptoms at 12 weeks post-acute infection. In one study that accounted for baseline symptom burden and appropriate comparators with no evidence of SARS-CoV-2 infection, most comorbidities in a list of 80 were associated with persisting symptoms at 12 weeks,[82] including physical comorbidities such as COPD (HR 1.55 (1.47–1.64) and mental health problems such as anxiety (HR 1.35 (1.31–1.39)).

A range of specific new diagnoses have also been described in populations following acute COVID-19. An investigation using the national healthcare databases of the US Department of Veterans Affairs (VA) and carefully selected control populations (with propensity score weighting to ensure balance in potential confounders), demonstrated a higher risk of incident symptoms and conditions spanning all body systems, beyond the first month of illness, in a cohort of mostly male patients.[83] Patients with COVID-19 were also at increased risk of developing most of these conditions compared with a historic population with seasonal influenza, increasing confidence that the findings might be attributable to SARS-CoV-2 infection specifically. New cardiovascular comorbidities have also been reported in those who survive the acute phase of COVID-19. In a large study with contemporary controls from the VA database, COVID-19 increased the risk of a composite outcome of any incident cardiovascular disease by 1.6 times, translating into an additional burden of new cardiovascular disease in 45 per 1000 people during the 12-month follow-up.[84] This increased risk did not vary substantially by pre-existing comorbidities, although only a limited number (including obesity, chronic kidney disease and diabetes) were assessed. This study also provided robust evidence for a relationship between increasing severity of acute COVID-19 (defined as non-hospitalized cases, hospitalized cases and those requiring ICU) and increased risk of incident cardiovascular disease.

The increased risk that comorbidities confer on developing both PASC and new comorbidities after acute COVID-19 have implications for policy and practice. Whilst vaccination is highly effective at preventing severe COVID-19 disease, early evidence indicates lower effectiveness in preventing PASC. In a recently published large study, vaccination reduced risk of PASC by only 15% after breakthrough infection, with vaccine effectiveness marginally lower in the one comorbid subgroup (individuals with immunosuppression) that was evaluated.[85] For this reason, there is likely to be an ongoing role for non-pharmacological interventions to reduce risk of exposure to the virus, as well as maintaining prioritisation of vaccination with booster doses for people with comorbidities. Comorbid individuals who develop COVID-19 may require closer follow up by clinicians, to ensure appropriate management through post-acute COVID-19 services.

Multimorbidity

Most research relating to the impact of long-term conditions on COVID-19 has focussed on single comorbidities. However, one-third of adults globally are estimated to have two or more long-term conditions,[86] increasing to more than two-thirds in those aged 65 years or older.[87] In a large study of hospitalized COVID-19 populations in the UK, crude mortality in patients with multimorbidity was more than double that of those without multimorbidity (37.2% versus 17.3%), even after adjustment for demographic factors.[88]

Distinguishing common clusters of comorbidities in patients with severe COVID-19 might help to identify common drugable mechanisms, as well as groups at particularly high risk of poor outcomes. Among 1706 of 360,283 participants in the UK Biobank with severe SARS-CoV-2 infection (defined as hospitalization),[89] 25.3% were multimorbid, defined from a list of 12 comorbidities. The combination of stroke and hypertension was most prevalent, and the combination of chronic kidney disease and diabetes was associated with the highest risk of severe COVID-19 (odds ratio (OR) 4.93; 95% CI 3.36–7.22). Clusters of cardiometabolic conditions, such as obesity, diabetes and chronic cardiac disease, are associated with both COVID-19 severity and cardiovascular complications,[90,91] raising the possibility of underpinning mechanisms related to chronic low-grade inflammation.[92]

In addition to clusters of conditions revealing potential biological mechanisms, interactions between demographic and socioeconomic factors, ethnicity and environment also influence the likelihood of infection and subsequent outcomes. This highlights limitations to current approaches, which often isolate biomedical investigation from social context. A broader lens is needed to understand the full complexity and mechanisms leading to poor outcomes in COVID-19 in relation to comorbidity and multimorbidity.[93] From a public health perspective, the increasing prevalence of multi-morbidity and the associated increased susceptibility to infectious disease such as COVID-19 underscores the need to improve baseline health to mitigate the impact of future epidemics and pandemics. Whilst some risk factors such as iatrogenic immunosuppression are not directly modifiable, others such as obesity can be, and addressing these also requires efforts to reduce the socioeconomic inequalities that underpin them. The net effect of COVID-19, non-communicable diseases associated with adverse outcomes, and the socioeconomic basis to non-communicable disease prevalence can be considered a 'syndemic'.[93,94]

From a health service perspective, clinical management of patients with multimorbidity is often complex. Multimorbidity can increase the risk of harm arising through clinical interventions.[95] In addition, multimorbidity is associated with lower likelihood of survival, and, even in those who survive, a greater risk of impaired quality of life.[96] This means that clinical guidelines for COVID-19 management need to be interpreted with nuance and require tailoring to individual circumstances. Furthermore, an individualized, careful balance of benefits and potential harms of treatments is needed, particularly when considering initiation of invasive, potentially burdensome treatments.

Future directions and conclusions

Identifying causal relationships between co-morbidities and outcomes in COVID-19 is methodologically difficult but scientifically important. In particular, a deeper understanding of the causal relationships between clinically-relevant traits and comorbidities, and disease outcomes in Covid-19, may reveal new molecular mechanisms and opportunities for new or repurposed therapeutics. Host genetics techniques, including Mendelian randomisation, will help to eliminate confounding in these relationships. More intensive efforts are required to define the mechanistic relationships between comorbidities in epidemiological, host genetics and laboratory research.

Recognition of the differeces between the three phases of disease in Covid-19 may enable future research to distinguish the specific impact of comorbidities on distinct mechanistic pathways. The impact of most common comorbid illnesses is likely to operate through a combination of defective resistance, defective tolerance, and the generic effect of frailty and reduced functional reserve. In this context, public health efforts to improve baseline population health are an integral part of

pandemic preparedness. In particular, the substantial burden of disease created by PASC, and the wider public health implications of the 'syndemic' of Covid-19 on top of widespread comorbidity due to common non-communicable disease and socioeconomic inequality merit urgent attention.

Ongoing evolution of SARS-CoV-2, the potential for co-infections with other seasonal pathogens such as influenza, and altered baseline host resistance due to vaccination mean that patterns of disease will continue to change. The significant effect of comorbidity on disease outcome is likely to persist and should remain a research priority.

Acknowledgements

Text Boxes

Box 1: Stages of COVID-19 pathogenesis

1. *Early viral illness*: viral replication is maximal in the upper respiratory tract but occurs throughout the body, including the gastrointestinal tract; there is no impairment of lung oxygenation function yet. Control of replication requires a functional type 1 interferon response and initiation of adaptive humoral and cellular responses. This phase is associated with fever, malaise, myalgia, enteric symptoms and upper respiratory tract symptoms.
2. *Inflammatory lung injury*: although viral load is an essential precipitant, innate immune-mediated lung injury (monocyte/macrophage-driven) occurs even in the absence of ongoing viral replication in the lung. This phase is associated with shortness of breath, cough and hypoxaemic respiratory failure. It is generally responsive to anti-inflammatory therapies (dexamethasone, interleukin-6 receptor blockers, JAK inhibitors).

- People who progress to the late inflammatory stage and require prolonged organ support in intensive care may experience non-specific complications, including myopathy, neuropathy, complications of organ support (e.g. ventilator-induced lung injury) and secondary infections (e.g. ventilator-associated pneumonia).

3. *Post-acute sequelae*: prolonged symptoms occur in a sub-group of surviving patients. This phase is associated with debilitating long-term symptoms (e.g fatigue, neurocognitive impairment, respiratory symptoms) that overlap with post-intensive care syndrome. Non-resolving inflammation is a feature, but the syndrome is mechanistically heterogeneous.

Box 2: Mendelian Randomization as a tool to test causality

Mendelian randomization uses genetic variants as instrumental variables in observational studies, to determine causality of relationships between risk factors and outcomes. For example, in 2020 the GenOMICC study studied a range of genetic variants that were already known to be associated with higher or lower levels of the tyrosine kinase protein TYK2. Since an individual's genetic code predisposes them to having more or less TYK2 expressed in their cells, and the assignment of genetic code at conception is random and not influenced by confounding variables, the question can be asked: what is the effect of increasing TYK2 levels on risk of critical Covid? Testing for relationship between TYK2-associated variants and risk of critical Covid provides a test of the hypothesis that TYK2 plays a causal role in pathogenesis of critical Covid.[7] This example also

demonstrates a key limitation of Mendelian randomisation: some of the Covid-associated variants affecting TYK2 expression, are also associated with changes in the protein sequence and function, which may provide an alternative mechanism. Nonetheless, the evidence from this analysis was the key factor that determined the decision to test a TYK2 and JAK-kinase inhibitor, baricitinib, in the RECOVERY trial, which ultimately found that it was an effective new treatment for severe Covid-19.[97] To our knowledge, this is the first example of a host genetic discovery leading to a new drug treatment in infectious disease or critical care medicine.

This same principle can be used to ask more complex questions about the mechanistic relationships between diseases. Where there is existing knowledge of a range of genetic variants associated with a particular comorbidity, Mendelian randomisation provides a test of the causal hypothesis: does that comorbidity cause severe Covid?

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