Epidemiological and Clinical Factors Modulating COVID-19

Subjects: Immunology

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Addressing factors modulating COVID-19 is crucial since abundant clinical evidence shows that outcomes are markedly heterogeneous between patients. This requires identifying the factors and understanding how they mechanistically influence COVID-19. While there is a multitude of factors modulating COVID-19. These modulating factors (MFs) were selected based on epidemiological and/or clinical studies to be representative of different categories: intrinsic (age, sex and genetic factors), co-morbidities (history of dyslipidemia, obesity, pre-existing heart failure and gut dysbiosis), lifestyle-related (vitamin D deficiency and diet) and environmental (air pollution and exposure to chemicals).

Keywords: Epidemiological ; COVID-19 ; Clinical

1. Introduction

In March 2020, the World Health Organization declared the first pandemic caused by a coronavirus [1]. Researchers worldwide have intensively investigated the biological mechanisms underlying the disease and the factors rendering some populations more vulnerable, resulting in a flood of publications. In the summer of 2020, the CIAO project (Modelling the Pathogenesis of COVID-19 using the Adverse Outcome Pathway Framework) was initiated to provide a unique overview of the available knowledge on COVID-19 pathogenesis using the Adverse Outcome Pathway (AOP) framework [2][3]. The AOP concept provides a pragmatic means for organizing fast-evolving scientific knowledge based on existing data and literature from different fields [2][4]. An AOP describes a sequence of biological events starting from an initial interaction at the molecular level, called Molecular Initiating Event (MIE), through key biological events up to an adverse outcome (AO) [5][6][7]. AOPs are not intended to describe all details, but rather capture essential events, called Key Events (KEs), which drive downstream KEs and ultimately the AO. Importantly, KEs must be measurable in laboratory or clinical settings. A significant distinguishing aspect of the AOP approach is the structured evaluation and representation of the weight of evidence supporting the causality of the relationships between two KEs, called Key Event Relationships (KERs) [8]. Available qualitative and quantitative information is considered in the KER weight of evidence evaluation, including the magnitude, direction, and time concordance of a perturbation in the upstream KE needed to elicit a detectable change in the downstream KE. Thus, a single AOP proposes one biological pathway leading to an AO and a set of methods to measure KEs and predict the AO. The Organisation for Economic Co-operation and Development (OECD) maintains an online platform called AOP-Wiki [9], where information captured in AOPs is openly accessible to interested researchers, regulators, and clinicians. It is important to mention that there is a rigorous approach to collect evidence at the core of AOP development; however, this approach does not rely integrally on systematic principles.

AOPs are widely acknowledged as valuable tools in chemical safety assessments and regulatory toxicology analyses to provide methods and predictive models [10] while minimizing animal testing. The utility of AOPs for regulatory application is defined by the confidence with which AOPs facilitate extrapolation of data measured at low levels of biological organization (molecular and cellular-based methods) to relevant outcomes in organs, individuals, or populations. AOPs can also be used for assessing the mechanistic plausibility of epidemiological observations, such as the relationships between exposure to chemicals or nanomaterials and risk for disease [11]. While currently mainly exploited in toxicology, AOPs could have great value for other fields, such as biomedical research, thus profiting from growing AOP networks that describe the effects of chemical and non-chemical stressors. Human diseases are generally classified based on clinical phenotypes. Transitioning to a mechanistically-based understanding of the diseases could facilitate the design of hypothesis-based research strategies, improve predictive modeling and contribute to drug discovery [8][12].

The CIAO project explores this broader application of AOPs by expanding it to a viral stressor, namely SARS-CoV-2 [2][3][13]. Within the project, many linear AOPs have been developed describing key steps leading to a specific AO in COVID-19

[14]. The AOP framework also considers modulating factors (MFs) that intervene at KERs, affecting the quantitative response-response relationship between two Kes [15]. Addressing MFs is crucial since abundant clinical evidence shows that COVID-19 outcomes are markedly heterogeneous. Patients range from being asymptomatic or having a mild upper respiratory illness to having severe lung injury that requires hospitalization and may progress to hyperinflammation, acute respiratory distress syndrome, multi-organ failure, and death [16][17]. The variation in clinical outcomes suggests that socio-demographic and biological factors, characteristic of individuals or populations, modulate the course of the disease, corresponding to the concept of the epidemiological triad in infectious diseases. A better understanding of these host-virus interactions could allow for the refinement of preventive measures and improvement of treatment options. This requires identifying MFs contributing to outcome heterogeneity and a mechanistic understanding of their influence on COVID-19.

2. Biological (Intrinsic)

Age. Age is by far the strongest risk factor for life-threatening COVID-19. Age distribution of COVID-19 deaths has been supported by multivariate analyses across continents [18][19]. The infection fatality ratio has been estimated to be lowest among 5- to 9-year-old children, with a log-linear increase in individuals older than 30 years [20]. Most deaths involved people older than 80 years, in particular in care facilities [21][22][23][24], while people over 65 years without co-morbidities have a very low COVID-19 mortality rate [25]. Surprisingly, infants and young toddlers seem protected from severe disease [26].

Sex. Epidemiological data and observational reports have shown that COVID-19 has different outcomes for men and women. Despite similar infection rates in men and women, men are at higher risk for hospitalisation, admission to an intensive care unit (ICU), and death [27][28]. COVID-19 outcomes are also influenced by gender differences, the different social roles and behavioural factors, but these aspects are not discussed here [29].

Genetic factors. Undoubtedly, host genetic factors also play a role in SARS-CoV-2 pathophysiology, influencing an individual or a population susceptibility [30][31]. Here, researchers aim to investigate the impact on COVID-19 of polymorphisms in **ACE2 and TMPRSS2**, serving as main SARS-CoV-2 cell entry gateways, as well as in Toll-like receptors (TLRs), acting as crucial actors of the immune system alert during infections. Epidemiological studies showed that around twenty natural ACE2 variants might partially account for the differences of COVID-19 prevalence and mortality rates observed between Europe and East Asia [32][33]. Regarding **TLRs**, it has been shown that certain patients with severe COVID-19 were associated with a rare putative loss-of-function variants of X-chromosomal TLR7, that causes poor defense against coronavirus [34][35]. Gene analysis also revealed elevated expression of TLR7 and TLR9, leading to exaggerated immune response, in certain ethnic groups with higher COVID-19 mortality [36][37]. Clinical evidence showing associations between TLR gain-of-function polymorphisms and higher incidence of ICU acquired infection have been reported for other immune-mediated diseases and infections [38][39][40]. In addition, patients with **blood group A** were reported to have an increased risk of severe COVID-19 while the protective effect of the O allele is small, with an odds ratio of ~0.90.

3. Pre-Existing Co-Morbidities

Atherogenic dyslipidemia and obesity. Beyond age, sex, and genetic factors, co-morbidities are the main clinical determinants of COVID-19 severity [17][41][42][43]. Particularly, COVID-19 patients with metabolic syndrome had significantly higher hospitalization and mortality rates [44][45]. Metabolic syndrome is the common denominator of hypertension, diabetes, obesity and dyslipidemia. Here, researchers will particularly investigate how a history of dyslipidemia and obesity impact COVID-19. Several studies reported associations between low HDL-cholesterol and elevated triglycerides (TG) in serum and severe COVID-19 [43][46][47][48][49][50]. This lipid signature is known as atherogenic dyslipidemia. In addition, many studies support that excess body weight is an important risk factor for severe COVID-19 [51][52]. One study found a linear increase in the risk of severe COVID-19, admission to the hospital and death, starting already at a Body Mass Index (BMI) > 23 kg/m^2, which is not attributable to excess risks of related diseases. This risk due to elevated BMI was particularly notable in people younger than 40 years of age [53]. However, a study in Costa Rica showed that the host co-morbidities are not specific of a particular clinical profile of patients during pre-vaccination time [54].

Pre-existing heart failure (HF). Early in the pandemic, reports exhibited that patients with pre-existing cardiovascular disease had increased mortality from COVID-19 [55]. A study in Italy showed that death was more than double in patients with cardiac disease, including HF, atrial fibrillation and coronary artery disease, compared to patients without cardiac pathologies [56]. HF is a chronic and progressive clinical syndrome in which the myocardium is unable to maintain an adequate cardiac output to meet the body needs for blood and oxygen as a consequence of structural and/or functional cardiac abnormalities [57]. Pre-existing HF was identified as a major factor leading to poorer prognosis in COVID-19

patients [56] and as a determinant for non-cardiovascular organ failure [58]. Approximately half of HF patients hospitalized for COVID-19 died (from all causes) [59], while 10% of the patients hospitalized for COVID-19 had a history of HF with higher levels of troponin (i.e., marker of myocardial injury) [60]. A recent meta-analysis confirmed that pre-existing HF is associated with higher mortality, worse prognosis and higher risk for hospitalization [61]. All this led people to investigate the mechanisms by which pre-existing HF modulate COVID-19.

Gut dysbiosis. Many studies show a link between COVID-19 and gut dysbiosis, defined as a reduction in gut microbial diversity and depletion of beneficial bacteria with enrichment of pathogenic microbes. Infection with SARS-CoV-2 directly alters the gut microbiota in mice, hamsters, and non-human primates [62][63][64]. Gut dysbiosis can thus be considered an AO caused by SARS-CoV-2. Studies in humans showed that COVID-19 patients exhibited fecal microbiome alterations at all times of hospitalization compared to controls [65][66][67][68]. In addition to being a consequence, a correlation between dysbiosis and severe COVID-19 has been shown in at least two human studies [65]. Compared to patients with mild symptoms, the gut microbiota of patients with severe COVID-19 showed lower Firmicutes/Bacteroidetes ratio, enrichment of Proteobacteria, and lowered abundance of beneficial butyrate-producing bacteria [69]. In addition, alteration of the gut microbiota was associated with several risk factors for severe COVID-19 [70]. This prompts people to explore how gut dysbiosis acts as a detrimental pre-condition in COVID-19 patients [64].

4. Lifestyle Factors

Diet. Dietary patterns, such as the “Mediterranean” or the “Western” diet, as well as certain foods, are proposed to impact COVID-19 prognosis and account—at least partially—for regional differences in death rates [71][72][73]. Epidemiological analyses highlighted a role for diet in disease prognosis in some cases. Severity was negatively associated with habitual intake of legumes, grains, breads, and cereals [73]. Two studies have associated a “Mediterranean” diet with lower risk of infection and severity [74][75]. Another study found an association between higher frequency of consumption of plant-based foods and lower risk of COVID-19, after accounting for social determinants of health, pre-existing conditions, and measures to reduce viral transmission [76]. However, another similar study with fewer participants found no association [76]. A growing awareness of the impact of diet on health requires an investigation of the effects of dietary intake—both nutrients and types of foods—on COVID-19 infection and prognosis. Here, researchers will explore the potential direct impacts of foods eaten regularly prior to infection but will not discuss the treatment of COVID-19 patients with food-derived compounds, or the effects of diet-related diseases on COVID-19.

Vitamin D deficiency. Vitamin D deficiency affects around half of the population worldwide [77][78]. Vitamin D deficiency prior to infection was shown to increase the risk of COVID-19 severity and mortality in most studies [79][80]. However, some data do not support a correlation between vitamin D deficiency and severity [81]. Conflicting results might be related to the complex interactions of vitamin D with the status of vitamins A and K, calcium, potassium and phosphorus [82]. Furthermore, some studies also suggest a correlation between supplementation of high levels of vitamin D and reduced hospital mortality in COVID-19 patients [83] or with reduced severity, but not mortality [84]. However, a recent Cochrane research found that strength of evidence about the beneficial effect of vitamin D supplementation in COVID-19 patients is low [85]. More research is needed to fully capture the impact of vitamin D on COVID-19. As low vitamin D status prior to infection appears as an impactful MF [79], it prompted people to investigate how a vitamin D deficiency interferes with COVID-19 underlying mechanisms and locate the current knowledge gaps and inconsistencies.

5. Environmental Factors

Air pollution. Air pollution covers a range of substances released into the atmosphere due to human activities, with some of the most prevalent and researched compounds including nitrogen oxides (NOx), ozone (O3), and fine particulate matter (PM2.5). The aggravating effects of these compounds on lung diseases are well-established [86], and the number of research speculating on a connection between air pollution and COVID-19 spread and mortality is growing [87][88][89][90]. At the same time, the direct effects of air pollution on the transmission of the virus are debated [91]. This association is often confounded with high population density and other factors known to affect the levels of transmission. While the positive relationship between air pollution and the transmission of the virus is still largely speculative, evidence points to air pollution as a MF increasing COVID-19 severity and mortality [88][90][92][93][94]. The AOP approach is a relevant and effective framework for investigating the mechanistic aspects of the correlations discussed above.

Chemical exposure, exemplified by PFAS. Humans are continuously exposed to a mixture of chemicals from different sources, such as from food, drinking water, and consumer products. A number of chemicals are known to cause adverse health effects, including impaired immunity, at current exposure levels [95]. Hence, it is reasonable to believe that exposure to certain chemicals may affect the response to COVID-19 [96]. Per- and polyfluoroalkyl substances (PFAS), a group of

several thousand widespread synthetic biopersistent and bioaccumulative chemicals sharing similar molecular structure (including Perfluorooctane sulfonic acid (PFOS) and Perfluorooctanoic acid (PFOA)) have been shown to cause negative effects on metabolism, thyroid function and the immune system [97], particularly when exposure occurs prenatally and/or during childhood [97].

Few studies have investigated correlations between PFAS exposure and COVID-19 thus far. A population living in a PFAS-contaminated region in Italy exhibited a higher mortality risk for COVID-19 [98]. In two regions heavily polluted by PFAS in China, a significant correlation between the urinary concentration of 12 PFAS and COVID-19 infection risk was reported [99]. Increased plasma-PFAS concentrations were associated with severe COVID-19 in Denmark, and this tendency remained after adjustment [100]. Finally, a study from the highly contaminated area in Sweden estimated that the incidence ratio of COVID-19 in the adult population was 1.19 compared to a reference population, suggesting a potential link between high PFAS exposure and susceptibility to COVID-19 [101]. More epidemiological studies are needed to assess the strength of the association between PFAS exposure and COVID-19 severity. However, PFAS exposure seems a plausible MF due to their immunotoxic properties and will be explored here as an example of how chemical exposure could modulate COVID-19 [102].

6. Therapeutic Intervention against COVID-19

The fast-spreading and disruptive nature of COVID-19 pandemic highlighted the need for rapid and reliable identification of therapeutic options. In the first phases of the health emergency, several hundreds of medications were trialed, creating a huge amount of data of divergent quality. However, only a small percentage of the proposed drugs showed to be effective against the virus [103]. Understanding the mechanisms underlying the disease is essential to propose adequate therapeutic interventions against COVID-19. Furthermore, drug repositioning rapidly emerged, being a quick and cost-effective solution to screen large libraries of candidate compounds [104]. Especially when the information on the molecular pathogenesis is limited, repurposing existing drugs has also the advantage of already proven safety profiles and known targets [105][106].

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