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Review

The pathophysiological mechanisms of COVID-19 and host immunity, with emphasis on the dysbiosis of the lung and gut microbiomes and pregnancy

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ABSTRACT

The coronavirus 2019 (COVID-19) pandemic is a health and economic crisis. It has also highlighted human relational problems, such as racism and conflicts between nations. Although vaccination programs against the severe respiratory syndrome coronavirus 2 (SARS-CoV-2) have started worldwide, the pandemic is ongoing, and people are struggling. The mechanism of disease severity in COVID-19 is multifactorial, complicated, and affected by viral pathogenesis. For example, monocyte dysfunction due to aging and respiratory and gut dysbiosis influence the host's immunity against SARS-CoV-2 including helper T-cell imbalance and viral clearance reduction, leading to accelerated disease progression in older patients or those with underlying diseases. The different immune responses against SARS-CoV-2 also contribute to various radiological findings, including that of acute respiratory distress syndrome, which is associated with high mortality, especially in patients susceptible to disease progression. We aimed to review the pathophysiological mechanisms involved in COVID-19, with emphasis on the altered microbiome in the lung and gut, and the different radiological findings in different patient groups, such as younger adults and pregnant women.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic followed the emergence of a novel coronavirus in Wuhan, China. The pathogen was later named the severe respiratory syndrome coronavirus 2 (SARS-CoV-2). The pandemic is a severe healthcare and economic crisis worldwide. Even after 2 years, as of January 2022, COVID-19 remains a threat to humankind [1–3]. To date, more than 308 million confirmed cases of COVID-19 have been reported in 220 countries, with more than 5.4 million confirmed deaths (as of 4:52 p.m. CET, January 11, 2022. https://covid19.who.int/). Although data from the WHO suggest that as many as 80% of infections are mild or asymptomatic, some patients have experienced pneumonia with respiratory failure [4]. Infected children and younger patients have been mostly asymptomatic or presented only mild symptoms. In these young patients, pneumonia is rare and tends not to progress in severity. It is well recognized that pneumonia due to COVID-19 typically shows bilateral ground-glass opacities (GGOs), while consolidation nor tree-in-bud appearance are not usually found [5,6]. In a previous study, we reported the clinical manifestations and chest computed tomography (CT) findings in a cohort of patients with COVID-19 pneumonia. Patchy shadows were found more frequently in patients aged 20–39 years than in older age patients (≧40 years) (50% vs. 8%, $p = 0.008$ by Fisher's exact test) [7]. We hypothesized that radiological findings of COVID-19 differ by age, and may explain the differences in disease severity and mortality. Moreover, we hypothesized that the aging-related monocyte dysfunction [8,9], lung and gut dysbiosis, and underlying chronic disease/s may influence host immunity and promote viral replication, resulting in high mortality in elderly patients with COVID-19. In this review, we focused on the correlation between disease severity and radiological findings, as well as examined how host immunity affected the lung and gut microbiome in patients with COVID-19.

2. Main text

2.1. *Epidemiology*

A viral pneumonia is caused by a viral infection. A previous study documented that viral pneumonia occurs with all respiratory viruses in 6–18% of patients [10]. SARS-CoV-2 has high pathogenicity. Severe acute respiratory distress syndrome can occur in patients with COVID-19. Of all cases, 13.8% are considered severe, and 6.1% have critical courses. The mortality rate is high. Approximately 12%–45% of patients with pneumonia require admission to the intensive care unit (ICU) [3,11]. The mortality rate was found to be particularly high in elderly patients aged 70 years or above in the USA and Japan, although the mortality rate differed in each country. Many risk factors that increase the severity and mortality of COVID-19 have been identified, including hypertension, malignancy, chronic respiratory diseases, smoking, obesity, and pregnancy [12].

2.2. *Reasons for the different mortality rates of COVID-19 in Japan and the US*

The mortality rate of COVID-19 in the US is remarkably higher than that in Japan. The Johns Hopkins University of Medicine reported that the number of patients who died because of COVID-19 in the USA was 849,241 per 64, 917, 963 confirmed cases (mortality rate 1.3%, 25,579 deaths/1,000,000 population). In contrast, Japan reported 18,423 deaths per 1,830,381 confirmed cases (mortality rate 1.0%, 1486 deaths/1,000,000 population) [13]. Several factors, such as the medical care system, lifestyle, and host immunity have been suggested for the difference in mortality between the two countries. First, the healthcare system in Japan is vastly different from that in the US. Japan has a universal national medical insurance in which all citizens can freely access care at any medical institution covered under medical insurance. In the US, accessing care from a medical institution has been challenging. The US CDC reported that 32.8 million Americans (12.1%) were uninsured in 2019, although the number is estimated to rise to 35 million by 2029 [14]. Second, obesity is an increased risk factor for disease severity in COVID-19 [15,16]. The prevalence of obesity (body mass index [BMI] > 30) among adults in the US is almost 10 times that in Japan [17,18]. Particularly, 9.2% of adult Americans are severely obese (BMI ≥ 40) [17]. The definition of obesity in Japan is BMI ≥ 25, which is also different from that in the US [19]. Third, the difference in gut dysbiosis can contribute to differing mortality rates between the two countries. Viral immunity is strongly correlated with gut dysbiosis, which is influenced by obesity and diet [9,14,20]. We now know that the gut microbiome is strongly influenced by age, sex, weather, and lifestyle including dietary intake, and that individuals from different countries have different gut

microbiomes [21,22]. The higher mortality rate in the US may be due to gut dysbiosis. We hypothesized that severe cytokine storms may be more common among American adults. These phenomena have also been used to explain why the mortality rate among patients with influenza was higher in the US than in Japan [23]. Lastly, the Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated vaccine against tuberculosis that is used globally, may be protective against SARS-CoV-2 infection and thereby, reduce the mortality rate [24]. Japan has a nationwide universal BCG vaccination program for infants. This may have exerted some protective effects against COVID-19. A previous report has confirmed that the mortality rate of COVID-19 in countries with BCG vaccination programs is lower than that in those without [25]. This is a current hot topic. We keenly await the results from current ongoing randomized control trials.

Additionally, the Japanese culture of frequent hand washing and wearing a face mask, less hugging, not kissing on the cheek as a greeting, and not wearing shoes indoors, may have minimized the transmission of SARS-CoV-2, and thus reducing the mortality rate.

2.3. *Radiological findings of COVID-19 pneumonia*

All respiratory viruses can lead to viral pneumonia. The frequency and severity depend on the virus itself. It is quite difficult to determine the causative pathogen by radiological findings alone [10]. Computed tomographic findings of COVID-19 pneumonia typically show GGOs, peripheral distribution, and bilateral lung involvements, and rarely, the tree-in-bud appearance or consolidation [5,6]. We have already reported that radiological findings may differ in patients of different ages. Younger patients with COVID-19 pneumonia are more likely to present with patchy lesions than elderly patients [1]. These radiological differences may be influenced by host immunity. In turn, host immunity may affect pathogenesis. Thus, radiological findings could differ with different host immunity, even though it is the same disease caused by the same pathogen. For example, *Mycoplasma pneumoniae* pneumonia has various radiological presentations depending on the type and degree of host immunity. The disease severity and radiological findings are correlated and caused by the cytokine balance of type I helper T cell (Th1) and type II helper T cell (Th2) [26]. Moreover, *Pneumocystis jirovecii* pneumonia shows a worse prognosis in non-human immunodeficiency virus (HIV) patients than in those infected with HIV [7,27]. Several theories have been suggested regarding different radiological patterns and outcomes in patients with COVID-19 of different ages. Not only viral pathogenesis, but also aging-related monocyte dysfunction and dysbiosis of the lung and the gut may contribute to the high mortality rate in elderly patients with COVID-19.

2.4. *Respiratory and gut dysbiosis*

The healthy lung and gut microbiome contribute to appropriate immune responsiveness and homeostasis in the human body. The theory of the lung-gut axis could explain these phenomena. Like other respiratory viral infections, the disease severity of COVID-19 is strongly correlated with dysbiosis of the gut-lung axis. Particularly, viral immunity is closely related to the gut microbiome. Hagen et al. suggested that gut dysbiosis impairs vaccine immunity. In their study, they administered broad-spectrum antibiotics to healthy adults prior to the seasonal influenza vaccine. Their results demonstrated significant impairment in H1N1-specific neutralization and in binding IgG1 and IgA [28]. Bradley et al. proposed that "the microbiota-driven interferon signature in lung epithelia impedes early virus replication and that type I interferon α/β receptor surface levels fine-tune this signature. Moreover, both murine and human studies revealed that antibiotics use could decrease pulmonary IgA production and increase the risk of pneumonia" [29]. The gut microbiome of patients with COVID-19 showed significantly reduced bacterial diversity, a higher relative abundance of opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces*, and a lower abundance of beneficial symbionts as compared to the control group. Moreover, it has been reported that the disease severity of COVID-19 is correlated with a predominance of opportunistic pathogens and inversely correlated with the abundance of beneficial commensals [30,31]. Schult et al. reported that gut dysbiosis is associated with disease severity and progression in patients with COVID-19 [32]. They also found that a stable microbial composition may contribute to a more favorable outcome. Specific taxonomic changes in the relative abundance of individual bacteria were correlated with complications, such as acute respiratory distress syndrome (ARDS) and acute kidney injury (AKI), hemodialysis, and acute cardiac events. Interestingly, *Faecalibacterium prausnitzii* was significantly reduced in patients with ARDS, AKI, hemodialysis, and acute cardiac events, and was negatively associated with mortality [32]. Ren analyzed the oral and fecal microbiome of patients with COVID-19 and reported that oral and fecal microbial diversity was reduced compared to healthy controls. Furthermore, butyric acid-producing bacteria were decreased, and lipopolysaccharide-producing bacteria were increased in the oral cavity of patients with COVID-19 [33].

The lung microbiome has several roles in viral immunity. First, microbiota dwelling on the respiratory surface can act as a barrier, therefore preventing viral attachment to the host cells. Second, it primes the lung's immunity against viral infections. Exposure to a diverse range of microbiota may also build up immunity. Focusing on the alternation of microbiota, a reduction in fecal bifidobacteria has often been mentioned for age-related gut dysbiosis [34]. Besides, butyrate-producing organisms from the *Clostridium* cluster XIVa and a reduction in anti-inflammatory organisms such as *F. prausnitzii* and *Akkermansia muciniphila* have also been reported [35]. Lung dysbiosis in patients with chronic respiratory diseases compared to the general population has been observed and reported [36–39]. Current evidence has highlighted that gut dysbiosis has an inflammatory effect on the joints, liver, or brain, influencing disease progression through the gut-joint axis [40], gut-liver axis [41], and gut-brain axis [42], respectively. This further suggests that patients with underlying diseases, such as rheumatoid arthritis, chronic liver disease, and neurologic disease, have gut dysbiosis, and that gut dysbiosis is involved in the disease progression of COVID-19 (Figs. 1 and 2).

The lung and gut microbiome may be critical in severe COVID-19 cases. In summary, dysbiosis of the lung and gut may affect the disease severity of COVID-19 and prognosis [33]. The lung and gut microbiome may be a potential therapeutic target for COVID-19.

2.5. *COVID-19 pneumonia in pregnant patients*

Pregnant patients are unique. They are of particular interest during the COVID-19 pandemic because expecting mothers are typically young and healthy. However, pregnancy presents an altered immunological state. Like the seasonal influenza virus infection [24], it is found that pregnant patients infected with severe acute respiratory syndrome coronavirus 1 showed a high risk of spontaneous abortion, preterm birth, and maternal death. However, follow-up postnatal testing of neonates did not reveal serologic evidence of vertical transmission [43]. Pregnant women with COVID-19 are also considered to have an increased risk of disease severity and mortality. At the beginning of the COVID-19 pandemic, chest CT scans were frequently taken [44,45] despite routine exposure to ionizing radiation being discouraged during pregnancy. In a systematic review of CT findings among 427 pregnant patients, Rachel et al. reported expecting mothers showed different tomographic findings compared with the general population [46]. In this study, the mean age was 30.4 years (range 17–49 years), which is the expected age range for pregnant women. In the CT images of these pregnant women, 69% bilateral involvements and 77% GGOs were seen. Of note, consolidation and pleural effusions were seen in 41% and 30%, respectively, which seems proportionally higher than that of the general population (Table 1). This may be due to the need for mother and fetus' needs to ensure immune tolerance to prevent fetal rejection during pregnancy [47,48]. This innate human immunity to protect a pregnancy could promote viral replication in the expectant mother, resulting in a cytokine storm [5,49]. Moreover, pregnant patients have expanded thoracic cages with splaying and a reduced functional residual capacity due to the expansive volume of the gravid uterus [50]. These anatomical and immunological changes contribute to the different radiological presentations compared with the general population and a poor prognosis among pregnant patients with COVID-19. Furthermore, hypertension, diabetes mellitus, and thrombosis during pregnancy may further lead to unfavorable outcomes.

In a review of neonatal outcomes [46], 251 neonates were tested for SARS-CoV-2 infection by reverse transcription-polymerase chain reaction (RT-PCR) and/or cases IgG antibody testing, resulting in a 96.8% negative test rate. Eight cases of suspected neonatal infection were reported. Six of which

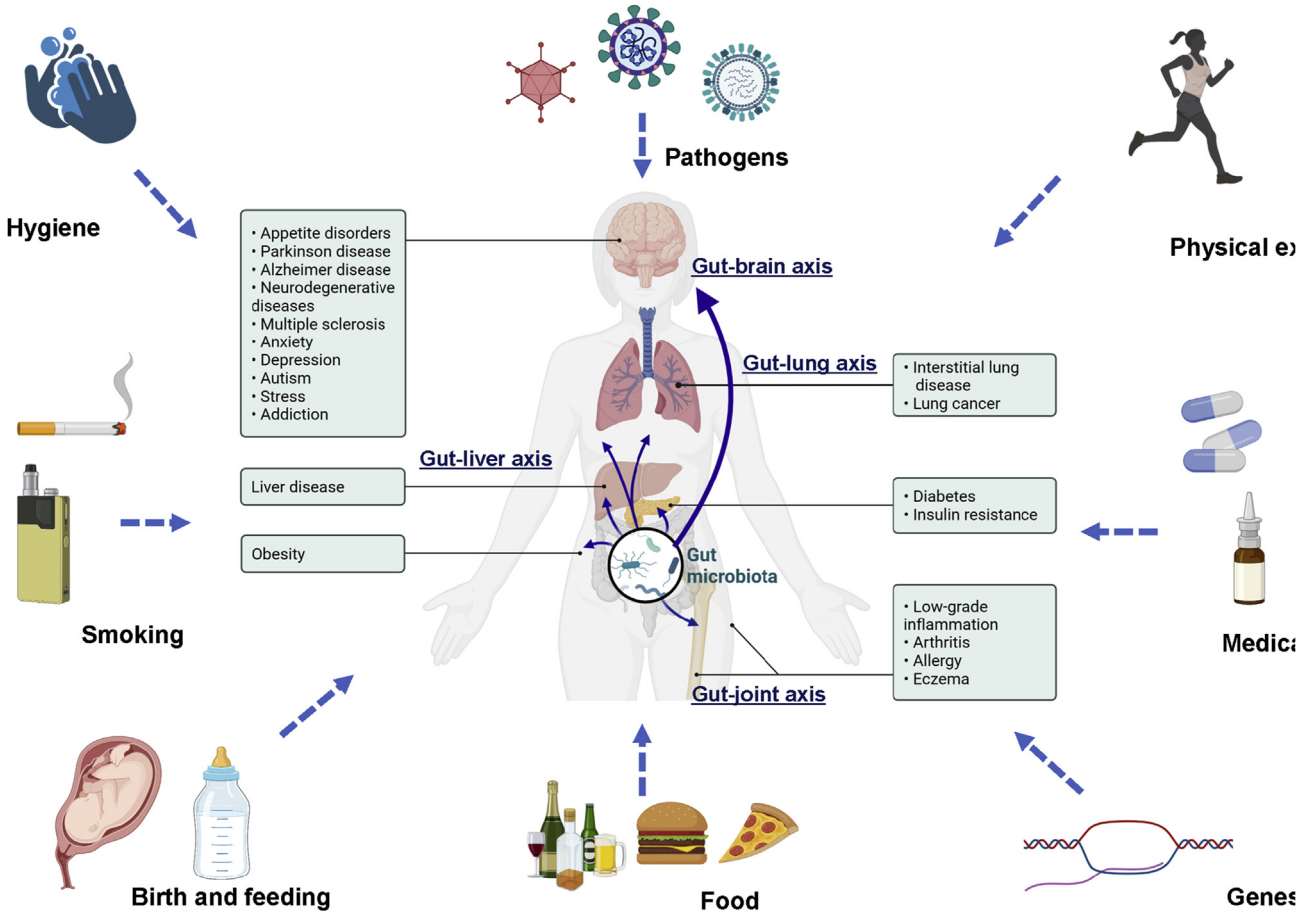

Fig. 1 – Correlation between dysbiosis and lifestyle factors, such as hygiene, food, alcoholic beverages, birth and feeding, physical exercise, smoking, stress, pathogens, medications, and genes. Gut dysbiosis correlates with the brain, lung, liver, and joints, mutually called the gut-brain axis, gut-lung axis, gut-liver axis, and gut-joint axis, respectively.

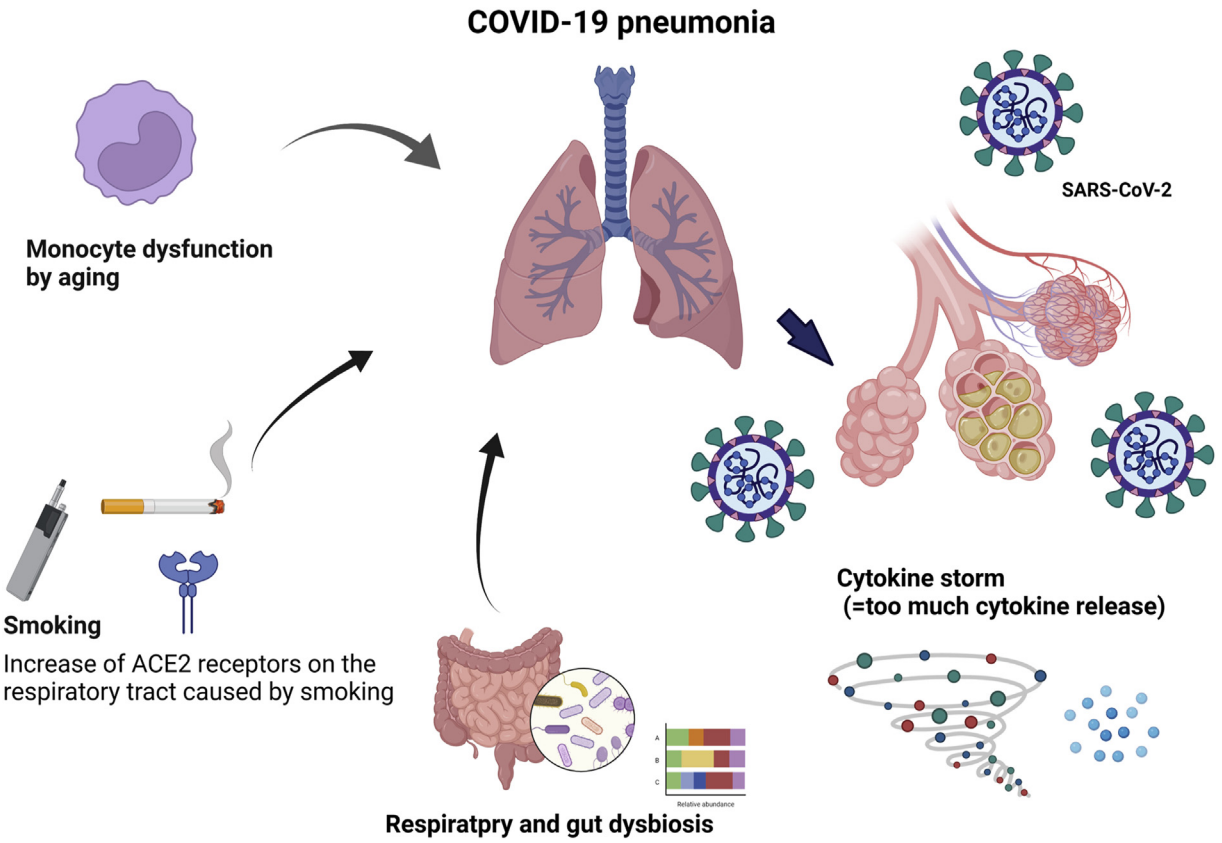

Fig. 2 – Pathological mechanism of disease progression in COVID-19 patients. Disease progression is accelerated by aging-related monocyte dysfunction, smoking history, and dysbiosis of the lung and gut. These figures were created using BioRender (https://biorender.com).

Table 1 – Comparison of radiological tomographic findings between pregnant patients and the general population.

Imaging findings	Pregnant patients (%)	General population (%)
Bilateral involvement	69.4	79.0–87.5
Peripheral distribution	68.1	76.0–100
Posterior involvement	72.5	80.4
Multi-lobar involvement	71.8	78.8
Ground-glass opacities	77.2	88.0
Consolidation	40.9	21.0–31.8
Pleural effusion	30.0	5.0

Data are cited in Ref. [49].

showed positive results of RT-PCR, and two tested positive by IgG antibody assay. The overall survival rate was 93%.

In conclusion, viral immunity affected by lung and gut dysbiosis and age-associated monocyte dysfunction can increase disease severity in humans. Radiological findings and COVID-19 prognosis may differ by age.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interest

The authors have no conflicts of interest.

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Author contributions

NA, HK, and HM conceptualized the article. NA drafted the manuscript. HM edited the draft and supervised the article. All authors read and approved the final manuscript.

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