Diagnostic Pathology: Open Access

Asai and Mikamo. Diagn Pathol Open 2021, 6:4

Mini Review Open Access

A Review on COVID-19 Severity from the Point of Radiological Findings and Host Immunity including Microbiome: Mini-Review

Nobuhiro Asai[1,2] and Hiroshige Mikamo[1*]

[1]*Department of Clinical Infectious Disease, Aichi Medical University Hospital, Aichi, Japan*
[2]*Department of Pathology, University of Michigan, Ann Arbor, MI, USA*

Abstract

Background: The pandemic of coronavirus infection 2019 (COVID-19) causes not only a health and economic crises, but also reveals a human relations problem such as racism and a conflict between nations. In Japan, we face several problems; The Tokyo Olympics 2020 was postponed to 2021, the emergence of social distancing enforcers, discrimination against medical staff who provide medical care for the patients with COVID-19 and misleading information by the mass media regarding COVID-19 vaccines. COVID-19 is not solely a viral disease, but a social problem that is caused by other factors. Because it is a social problem, the mechanism of disease severity in COVID-19 is multifactorial, complicated and is affected by viral pathogenesis as well as by host immunity. We describe the review focusing on the multiple factors which could cause disease severity of COVID-19.

Main text: All respiratory viruses could cause viral pneumonia, even though the frequency and severity depend on the virus itself. The mortality rate of COVID-19 differs in different ages as well as radiological findings in different age. It is well-known that radiological findings differ in host immunity, such as *Pneumocystis jirovecii* pneumonia (PJP), *Mycoplasma pneumoniae* pneumonia. These are affected by the imbalance of cytokine produced between type I and II of helper T-cell, showing a different prognosis. As for disease severity of COVID-19, there are several theories that COVID-19 patients show different radiological patterns and outcomes by age. Not only viral pathogenesis but also dysfunction of monocytes in aging and the lung and the gut dysbiosis could contribute to the high mortality rate in elderly patients.

Conclusion: Viral immunity affected by lung and gut dysbiosis and age-associated monocyte dysfunction could cause disease severity in humans. We hypothesize that radiological findings and prognosis of COVID-19 differ by aged-group.

Keywords: COVID-19; SARS-CoV-2; Pneumonia; Lung and gut dysbiosis; Gut-lung axis; Pregnancy

Abbreviations: ARDS: Acute Respiratory Distress Syndrome; COVID-19: Coronavirus Infection 2019; CT: Computed Tomography; GGO: Ground-glass Opacities; HIV: Human Immunodeficiency Virus; HLA-DR: Human Leukocyte Antigen-DR isotype; ICU: Intensive Care Unit; MPP: *Mycoplasma pneumoniae* pneumonia; PJP: *Pneumocystis jirovecii* pneumonia; RT-PCR: Reverse Transcription Polymerase Chain Reaction; SARS-CoV-1: Severe Acute Respiratory Syndrome Coronavirus 1; SARS-CoV-2: Severe Respiratory Syndrome Coronavirus 2; Th1: type I helper T cell; Th2: type II helper T cell

Introduction

The pandemic of coronavirus disease 2019 (COVID-19) followed the emergence of a novel corona virus in Wuhan, China, causing severe respiratory syndrome coronavirus 2 (SARS-CoV-2). This caused a severe crisis in healthcare as well as in the economy worldwide and is still threatening at this time of March 2021 [1-3]. To date, more than 119 million confirmed cases of COVID-19 have been reported in 220 countries, with more than 2.6 million confirmed deaths as of 5:13 pm CET, 14 March 2021. 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]. Children and younger patients are mostly asymptomatic or present mild symptoms, and they rarely have pneumonia which can become severe. It is well-known that COVID-19 pneumonia typically shows bilateral involvement or ground-glass opacities (GGO)s, but neither consolidation nor tree-in-bud appearance [5,6]. We previously reported on a cohort of clinical manifestations and radiological findings by chest computed tomography (CT) among COVID-19 pneumonia patients. Patchy shadows were found more frequently in 20-39 year old-patients than in others (≧ 40 years) (50% *vs.* 8%, p=0.008 by Fisher's exact test) [3]. We hypothesize that radiological findings of COVID-19 could differ by age, resulting in different disease severity and mortality. We also think that dysfunction of monocytes in aging, the lung and gut dysbiosis and underlying disease could influence host immunity and promote viral replication, resulting in high mortality in the elderly (Figure 1). This review focuses on the correlation between disease severity and host immunity in COVID-19 patients.

***Corresponding author:** Hiroshige Mikamo, Department of Clinical Infectious Diseases, Aichi Medical University School of Medicine, 480-1195 1-1 Yazakokarimata, Nagakute, Aichi, Japan, E-mail: mikamo@aichi-med-u.ac.jp

Received: May 03, 2021; **Accepted:** May 17, 2021; **Published:** May 24, 2021

Citation: Asai N, Mikamo H (2021) A Review on COVID-19 Severity from the Point of Radiological Findings and Host Immunity including Microbiome: Mini-Review. Diagnos Pathol Open 6: 191.

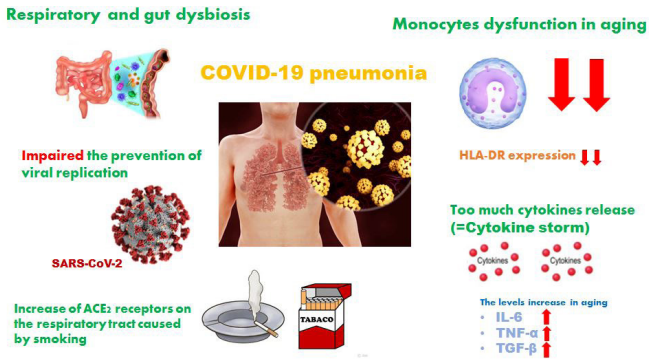

Figure 1: The mechanism of disease severity on COVID-19.

Literature Review

Epidemiology

DBasically, a viral infection could cause viral pneumonia. A previous study documented that viral pneumonia can occur with all respiratory viruses in 6% to 18% of patients [7]. SARS-CoV-2 has high pathogenicity and COVID-19 could present severe acute respiratory distress syndrome (ARDS), resulting in 13.8% cases with severe, and 6.1% with critical courses, showing a high mortality rate of 12%-45% among cases with pneumonia requiring intensive care unit (ICU) admission [2,8]. Especially, it was found that the mortality rate was high in elderly patients aged 70 years or older in the USA as well as in Japan (Figures 2 and 3). Even if the mortality rates differ in each country. As for the risk factors of COVID-19 in terms of the disease severity, it is well-known that hypertension, malignancy, chronic respiratory diseases, smoking, obesity, and pregnancy are risk factors for disease severity and death [9,10].

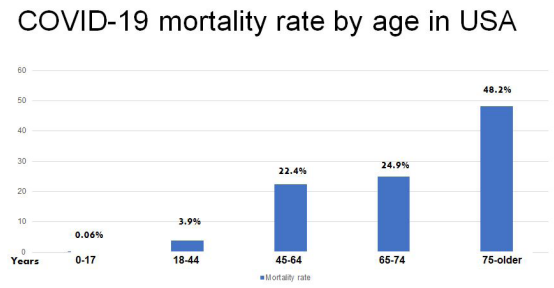

Figure 2: The mortality rate of COVID-19 by age in the USA.

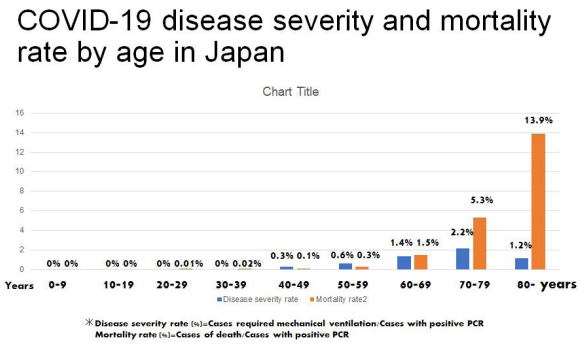

Figure 3: The mortality rate of COVID-19 by age in Japan.

Radiological findings of COVID-19 pneumonia

All respiratory viruses could cause viral pneumonia in Table 1, even though the frequency and severity depend on the virus itself. It is quite difficult to determine the causative pathogen by radiological findings alone [11]. Computed tomographic findings of COVID-19 pneumonia typically show GGOs, peripheral distribution, and bilateral lung involvements, but not tree-in-bud appearance or consolidation [5,6]. However, we already reported that radiological findings could differ in different aged patients. Younger patients with COVID-19 pneumonia have patchy lesions more often than the elderly with the disease [3]. We hypothesize that these radiological differences could be affected by host immunity. It is well-known that radiological findings could differ in host immunity. Host immunity could be involved in the pathogenesis. Thus, radiological findings could differ with different host immunity, even though it is the same disease caused by the same pathogen. *Mycoplasma pneumoniae* pneumonia (MPP) has a variety of radiological pictures depending on the variety and degree of host immunity. The disease severity and radiological findings are correlated with the cytokine balance of type I helper T cell (Th1) and type II helper T cell (Th2) [12]. *Pneumocystis jirovecii* pneumonia (PJP) in non-human immunodeficiency virus (HIV) patients shows a worse prognosis than those infected by HIV [13,14]. There are several theories that COVID-19 patients show different radiological patterns and outcomes by age. Not only viral pathogenesis but also dysfunction of monocytes in aging and the lung and the gut dysbiosis could contribute to the high mortality rate in elderly patients.

Viruses linked to community-acquired pneumonia	
Respiratory syncytial virus	Hantavirus
Rhinovirus	Parechoviruses
Influenza A, B and C virus	Epstein-Barr virus
Human metapneumovirus	Human herpes virus 6 and 7
Parainfluenza virus types 1, 2, 3, and 4	Herpes simplex virus
Human bocavirus	Mimivirus
Enteroviruses	Cytomegalovirus
Varicella-zoster virus	Measles

Table 1: Viruses linked to community-acquired pneumonia in children and adults [7].

Monocyte dysfunction in aging

Monocytes play an important role in the more severe COVID-19 that occurs in the elderly [15]. Aging has been reported to be characterized by substantial dysregulation of various cellular functions in monocytes and macrophages. Monocytes isolated from the elderly show increased basal cytokine production compared to the younger ones [16]. In addition, monocytes in the elderly also exhibit impaired phagocytosis and decreased expression of the human leukocyte antigen-DR isotype (HLA-DR) [17,18]. "Down-regulation of HLA-DR in monocytes and other antigen-presenting cells can suppress the transition to an adaptive immune response during acute infection and thus exacerbate the disease." In fact, Giamarellos-Bourboulis, et al. An observational study of 54 individuals with COVID-19 found "evidence of severe immunodysregulation caused by monocyte dysfunction in all patients" [19]. We speculate that monocyte dysfunction may contribute to the severity of more diseases of COVID-19 in the elderly.

Respiratory and gut dysbiosis

The healthy lung and gut microbiome contribute to appropriate

immune responsiveness and maintain homeostasis in the human body. Particularly, viral immunity is associated with the gut microbiome. Hagen, et al. suggested that gut dysbiosis impairs vaccine immunity. They administered broad-spectrum antibiotics to healthy adults prior to the seasonal influenza vaccine. Then, there was significant impairment in H1N1-specific neutralization and binding IgG1 and IgA response [20]. 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 [21]. Moreover, both murine and human studies revealed that antibiotics use could decrease pulmonary IgA production and increase the risk of pneumonia". These phenomena could be explained by the theory of the lung-gut axis. Like other respiratory viral infections, the disease severity of COVID-19 is strongly correlated with gut and lung dysbiosis.

The gut microbiome of COVID-19 patients had a significant reduction of bacterial diversity, a significantly higher relative abundance of opportunistic pathogens such as Streptococcus, Rothia, Veillonella, and Actinomyces, and a lower abundance which are beneficial symbionts as compared to the control group. Moreover, it has been reported that the disease severity of COVID-19 is correlated with the predominance of opportunistic pathogens and inversely with the beneficial commensals [22,23].

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 lung immunity, which will fight against viral infection, and the exposure to a diverse range of microbiota may build a wider immunity. Focusing on the alternation of microbiota, a reduction in fecal bifidobacteria has often been mentioned for age-related gut dysbiosis [24]. Besides, butyrate-producing organisms from the Clostridium cluster XIVa has been reported as well as a reduction in anti-inflammatory organisms such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila* [25]. Some already reported that the lung dysbiosis in patients with chronic respiratory disease compared to the general population, has been observed [26-28]. Dickson et al. reported that the lung microbiome could predict the clinical outcome and death in severely ill patients [29]. This study showed that increased lung bacterial burden and lung enrichment with gut-associated bacteria were predictive of an adverse consequence of acute respiratory distress syndrome (ARDS). Thus, the lung microbiome might have a critical role in severe COVID-19 cases. In summary, the lung and gut dysbiosis affect the disease severity of COVID-19 and prognosis. The lung and gut microbiome may be a potential and therapeutic target for COVID-19 shortly.

COVID-19 pneumonia in pregnant patients

Pregnant patients are a very unique population of interest during the pandemic of COVID-19 as they are typically young, otherwise healthy individuals. Pregnant patients have altered immunological states due to expectancy. Like seasonal influenza virus infection [30], it is found that pregnant patients infected with Severe Acute Respiratory Syndrome coronavirus 1 (SARS-CoV-1) showed a high risk of spontaneous abortion, preterm birth, and maternal death. However, follow-up testing on neonates postnatally was unable to detect serologic evidence of vertical transmission in the cohort [31]. COVID-19 is also considered to be an increased risk of disease severity and death among pregnant women. At the beginning of the COVID-19 pandemic, chest CT scans were frequently taken in many patients [32,33], 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 that pregnant patients showed different patterns of tomographic findings in comparison to the general population [34]. The mean age was 30.4 years (range 17-49 years), which is not uncommon for pregnant women. As for the CT findings, 69% and 77% of bilateral involvements and GGOs were seen in pregnant patients. Of note, consolidation and pleural effusions were seen in 41% and 30% respectively, which seems proportionally higher in comparison to the general population (Table 2). This could be explained by the fact that mother and fetus should be balanced with the need for immune tolerance to prevent fetal rejection during pregnancy [35,36]. This kind of human immunity to retain a pregnancy in pregnant patients could promote viral replication, resulting in a cytokine storm [5,37]. Besides, pregnant patients have expanded thoracic cages with splaying and reduced functional residual capacity due to the expansive volume of the gravid uterus [38]. These anatomical and immunological changes could cause different radiological findings from the general population and poor prognosis among pregnant patients with COVID-19. Pregnant patients could easily be complicated by hypertension, diabetes mellitus, and thrombosis, which contribute to the unfavorable outcomes.

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
Consolidation	40.9	21.0-31.8
Pleural effusion	30	5

Table 2: Comparison of radiological tomographic findings between pregnant patients and the general population.

As for neonatal outcomes in the review [34], 251 neonates were tested for SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) and/or cases IgG antibody testing, with a resulting 96.8% negative test rate. Eight cases of suspected neonatal infection were reported, six of which showed positive results of RT-PCR, and two of tested positive by IgG antibody assay. The overall survival rate was 93%.

Conclusion

Viral immunity affected by lung and gut dysbiosis and age-associated monocyte dysfunction could cause disease severity in humans. We hypothesize that radiological findings and prognosis of COVID-19 differ by aged-group.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

Not applicable.

Competing Interests

None declared.

Funding

None declared.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.
2. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR (2020) Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 55: 105924.
3. Asai N, Sakanashi D, Nakamura A, Kishino T, Kato H, et al. (2020) Clinical manifestations and radiological features by chest computed tomographic findings of a novel coronavirus disease-19 pneumonia among 92 patients in Japan. J Microbiol Immunol Infect 1182: 30168-30170.
4. World Health Organization (2020) Coronavirus disease 2019 (COVID-19) situation report 46.
5. Ye Z, Zhang Y, Wang Y, Huang Z, Song B (2020) Chest CT manifestations of new coronavirus disease 2019 (COVID-19): A pictorial review. Eur Radiol 30: 4381-4389.
6. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A (2020) Coronavirus Disease 2019 (COVID-19): A systematic review of imaging findings in 919 patients. Am J Roentgenol 215: 8787-8793.
7. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR (2011) Viral pneumonia. Lancet 377: 1264-1275.
8. World Health Organization (2020) Report of the WHO-China joint mission on Coronavirus disease 2019 (COVID-19).
9. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, et al. (2020) Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. Eur Respir J 55: 2000547.
10. Helvaci N, Eyupoglu ND, Karabulut E, Yildiz BO (2021) Prevalence of obesity and its impact on outcome in patients with COVID-19: A systematic review and meta-analysis. Front Endocrinol 12: 598249.
11. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR (2011) Viral pneumonia. Lancet 377: 1264-1275.
12. Yang M, Meng F, Gao M, Cheng G, Wang X (2019) Cytokine signatures associate with disease severity in children with *Mycoplasma pneumoniae* pneumonia. Sci Rep 9: 17853.
13. Asai N, Motojima S, Ohkuni Y, Matsunuma R, Nakashima K, et al. (2012) Early diagnosis and treatment are crucial for the survival of Pneumocystis pneumonia patients without human immunodeficiency virus infection. J Infect Chemother 18: 898-905.
14. Asai N, Ohkuni Y, Matsunuma R, Otsuka Y, Kaneko N (2011) Radiological features of pneumocystis pneumonia (PCP) without HIV. Eur Respir J 38: p3669.
15. Pence BD (2020) Severe COVID-19 and aging: are monocytes the key? Geroscience 42: 1051-1061.
16. McLachlan JA, Serkin CD, Morrey KM, Bakouche O (1995) Antitumoral properties of aged human monocytes. J Immunol 154: 832-843.
17. Seidler S, Zimmermann HW, Bartneck M, Trautwein C, Tacke F (2010) Age-dependent alterations of monocyte subsets and monocyte-related chemokine pathways in healthy adults. BMC Immunol 11: 30.
18. Hearps AC, Martin GE, Angelovich TA, Cheng WJ, Maisa A, et al. (2012) Aging is associated with chronic innate immune activation and dysregulation of monocyte phenotype and function. Aging Cell 11: 867-875.
19. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, et al. (2020) Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 27: 992-1000.
20. Hagan T, Cortese M, Rouphael N, Boudreau C, Linde C, et al. (2019) Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. Cell 178: 1313-1328.
21. Bradley KC, Finsterbusch K, Schnepf D, Crotta S, Llorian M, et al. (2019) Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. Cell Rep 28: 245-256.
22. Zuo T, Zhan H, Zhang F, Liu Q, Tso EYK, et al. (2020) Alterations in fecal fungal microbiome of patients with COVID-19 during time of hospitalization until discharge. Gastroenterology 159: 1302-10.
23. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, et al. (2020) Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology 159: 944-955.
24. Ficara M, Pietrella E, Spada C, Della Casa Muttini E, Lucaccioni L, et al. (2020) Changes of intestinal microbiota in early life. J Matern Fetal Neonatal Med 33: 1036-1043.
25. Mangiola F, Nicoletti A, Gasbarrini A, Ponziani FR (2018) Gut microbiota and aging. Eur Rev Med Pharmacol Sci 22: 7404-7413.
26. O'Dwyer DN, Ashley SL, Gurczynski SJ, Xia M, Wilke C, et al. (2019) Lung microbiota contribute to pulmonary inflammation and disease progression in pulmonary fibrosis. Am J Respir Crit Care Med 199: 1127-1138.
27. Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, et al. (2011) Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. J Allergy Clin Immunol 127: 372-381.
28. Mayhew D, Devos N, Lambert C, Brown JR, Clarke SC, et al. (2018) Longitudinal profiling of the lung microbiome in the AERIS study demonstrates repeatability of bacterial and eosinophilic COPD exacerbations. Thorax 73: 422-430.
29. Dickson RP, Schultz MJ, van der Poll T, Schouten LR, Falkowski NR, et al. (2020) Lung microbiota predict clinical outcomes in critically ill patients. Am J Respir Crit Care Med 201: 555-563.
30. Asai N, Mikamo H (2021) Prophylaxis of influenza viral transmission: What is the current prophylaxis? Influenza.
31. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, et al. (2004) Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol 191: 292-297.
32. Demirjian NL, Fields BKK, Song C, Reddy S, Desai B, et al. (2020) Impacts of the Coronavirus Disease 2019 (COVID-19) pandemic on healthcare workers: A nationwide survey of United States radiologists. Clin Imaging 68: 218-225.
33. Demirjian NL, Fields BKK, Gholamrezanezhad A (2020) Role of Chest CT in Resource-Driven Healthcare Systems. AJR Am J Roentgenol 215: W36.
34. Oshay RR, Chen MYC, Fields BKK, Demirjian NL, Lee RS, et al. (2021) COVID-19 in pregnancy: A systematic review of chest CT findings and associated clinical features in 427 patients. Clin Imaging 75: 75-82.
35. Svensson J, Jenmalm MC, Matussek A, Geffers R, Berg G, et al. (2011) Macrophages at the fetal-maternal interface express markers of alternative activation and are induced by M-CSF and IL-10. J Immunol 187: 3671-3682.
36. Tang MX, Hu XH, Liu ZZ, Kwak-Kim J, Liao AH (2015) What are the roles of macrophages and monocytes in human pregnancy? J Reprod Immunol 112: 73-80.
37. Lam CM, Wong SF, Leung TN, Chow KM, Yu WC, et al. (2004) A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. BJOG 111: 771-774.
38. Lapinsky SE (2015) Acute respiratory failure in pregnancy. Obstet Med 8: 126-132.