Sys Rev Pharm 2020;11(2):703-713
A multifaceted review journal in the field of pharmacy

THE HIDDEN VULNERABILITY OF COVID-19 OBSERVED FROM ASYMPTOMATIC CASES IN INDONESIA

Brian Eka Rachman[1], Musofa Rusli[1], Muhammad Miftahussurur[2]*
[1]Infectious Tropics Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
[2]Gastroenterology and Hepatology Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Institute of Tropical Disease, Universitas Airlangga, Surabaya 60131, Indonesia

ABSTRACT

The world is currently overwhelmed by fighting a pandemic caused by the novel coronavirus (COVID-19). Within just a few months, the virus has spread all over the country causing many deaths. Although some guidelines have been proposed to prevent more casualties, the transmission rate remains high. One clinical spectrum that was initially being an underdog for its ability to widely spread COVID-19 is asymptomatic cases. Subtle clinical manifestations with the same transmission potential as in symptomatic cases make asymptomatic cases worth to be considered. Transmission of asymptomatic cases, commonly in family clusters, will also be a new problem considering some family members have a high risk of COVID-19. The asymptomatic cases remain a problem in developed and former countries infected with COVID-19, and also for Indonesia as a developing country with various uniqueness. Indonesia's authorities are struggling to win this battle with COVID-19 with all the available resources, and until now the stressing is still on symptomatic cases while asymptomatic cases can be a silent thread if not recognized and handled properly. A better and deeper understanding of various aspects of asymptomatic cases may be a consideration for better health policies.

Keywords: Vulnerability, asymptomatic, (COVID-19), SARS-Cov, infectious disease.

Correspondence:
Muhammad Miftahussurur, MD., Ph.D
Division of Gastroentero-Hepatology, Department of Internal Medicine, Faculty of Medicine, Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya 60131, Indonesia
Tel: +81-25-232-6840; Fax: +62-31-5023865
E-mail: muhammad-m@fk.unair.ac.id

INTRODUCTION

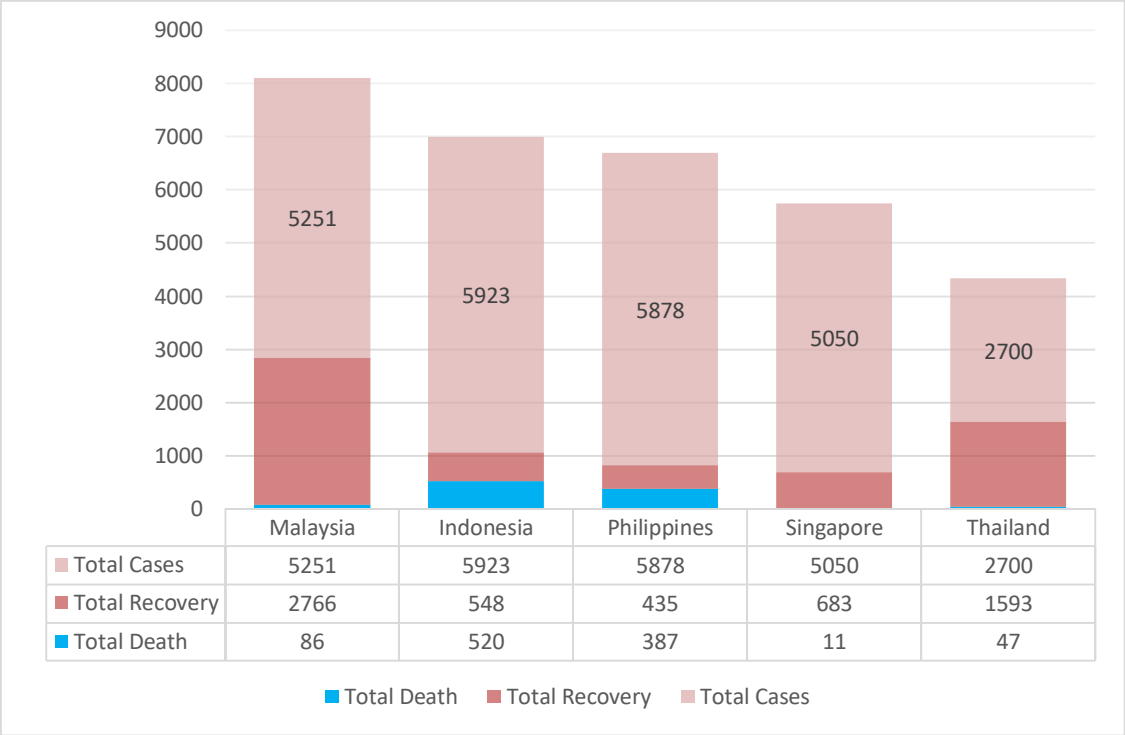
In late December 2019, an outbreak started from a patient with clinical manifestation of enigmatic pneumonia and it has been linked to the Huanan Seafood Wholesale Market, Wuhan. By January 2020, 44 similar cases were reported to World Health Organization (WHO) China with the same clinical manifestation as the ones identified in Wuhan and the causative agent remained unknown.[1] In the following weeks, more cases had been discovered with multiple clinical symptoms of fever, dry cough, dizziness, and occasional gastrointestinal symptoms, and throat swab samples were chosen to be used for diagnostic testing.[1–3] On January 7th, 2020, the Chinese Center for Disease Control and Prevention (CCDS) successfully identified the cause of those enigmatic pneumonia cases as a new type of coronavirus infected pneumonia (NCIP),[1–3] then was officially announced coronavirus disease as COVID-19, caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Within a short period, the outbreak has been spreading rapidly to other countries outside China such as Thailand, Japan, South Korea, Vietnam, Germany, the United States, and Singapore, forcing WHO to declare this outbreak as a pandemic on March 12, 2020.[1]

In less than a month, COVID-19 has been rapidly spreading in 210 countries in five continents with total cases of 2.206.690, of which 558.440 cases are recovered and 148.663 died. (Coronavirus live update, data obtained 17 April 2020, available at https://www.worldometers.info/coronavirus/). With a total case of 5.923, and 520 death cases made Indonesia has a higher mortality rate than cumulative COVID-19 cases worldwide (8.7% vs 6.73%), in fact, the highest in Southeast Asia (As depicted in Figure 1). The cause of such high death rates may vary but it was majorly affected by comorbidities and insufficiency of diagnostic testing, resulted in undetected cases remains circulating freely. It has been reported that more than 80% of COVID-19 cases defined as asymptomatic or having mild clinical manifestations, but still potentially be able to transmit to others and the mechanism of direct transmission remained unknown.[4]

The rapid increase of COVID-19 transmission is very alarming amidst the multiple efforts that have been applied by the authorities worldwide to control the recent outbreak. One major challenging obstacle is the rise of asymptomatic cases. The authorities have published a protocol for immediate screening for fever and respiratory upper respiratory tract infection for those who previously traveled to the affected area but this method remains ineffective to decelerate the COVID-19 transmissions. Recently a phenomenon of sample cluster case occurred as it was reported in China that 22 people visited a hospital to seek medical care without

realizing they have been infected with COVID-19. Those patients were infected by someone who had a traveling history but does not show any particular symptoms of COVID-19.[4] This current problem needs more urgent attention, as the risk of direct transmission is considerably high. The aim of this article is to focus on exploring the asymptomatic cases in COVID-19 patients and potential approaches to manage those cases.

Figure 1. Profile of the five highest number of COVID-19 cases in ASEAN* (Coronavirus live update, https://www.worldometers.info/coronavirus/country/indonesia/) *data obtained April 17, 2020



	Malaysia	Indonesia	Philippines	Singapore	Thailand
Total Cases	5251	5923	5878	5050	2700
Total Recovery	2766	548	435	683	1593
Total Death	86	520	387	11	47

ASYMPTOMATIC SPECTRUM

The clinical manifestations of COVID-19 are characterized by a broad spectrum range from asymptomatic, mild, moderate, severe tract infections, acute respiratory distress syndrome (ARDS), sepsis, septic shock, to atypical signs in geriatric.[5] To date, 80% of COVID-19 patients developed asymptomatic to mild symptoms.[4] Various reports worldwide showed various COVID-19 asymptomatic case rates diverse from 1.2% to 51.4% (shown in Table 1). The first asymptomatic COVID-19 case was an 8-month-old child in a family cluster in China as reported in December 2019. Additionally, another Chinese study informed that a family of five was positive COVID-19; probably they were infected from one asymptomatic family member who lives in Wuhan and recently visited their relatives in Anyang.[6] Most COVID-19 studies mainly focused on symptomatic cases; hence the data for asymptomatic cases are fairly limited. However, a study in China specifically reported on asymptomatic cases identifying some of the subjects (five out of twenty-four patients) were eventually showing symptoms after isolation and were admitted to hospital. COVID-19 developed a pattern in which the elderly patients tend to have a shorter incubation period compared to a younger age.[7,12] Most large-scale cases are identified through intensive screening, clustering, and contact tracing. Some reported cases are primary/imported, secondary contact (infected from primary contact), and tertiary contact cases (infected from secondary contact) (defined as tier 1, 2, and 3).[6–16]

In Indonesia, the asymptomatic case is defined as individuals without symptoms of COVID-19 but had a history of direct contact with confirmed COVID-19 patients. Asymptomatic cases are classified as low risk and high-risk (Ministry of Health, 3rd, and 4th edition of National Guidelines for COVID-19 Prevention and Control). Indonesian government not only reported the number of confirmed, recover, and death cases of COVID-19 transparently but also the numbers of people and patients under surveillance, although asymptomatic cases remain unofficially recorded. In Indonesia, asymptomatic cases become the major challenge for the authorities in terms of fighting against COVID-19. The fact that many COVID-19 infected cases did not have a clear contact history remains the biggest obstacle as it was related to the first confirmed cases in Depok on March 2, 2020. Still, other researchers had suspected that COVID-19 entered Indonesia before the official government announcement. Additionally, along with the increase in confirmed COVID-19 patients, several health centers had issues with the limited availability of personal protective equipment (PPE). To date, unfortunately the distribution of PPE has been reportedly still lacking and relatively rare in the market.

This issue has forced the medical staff to wear PPE below from the standard for COVID-19 protocols. Also, the government seemed rather slow to release official PPE etiquettes right after the first confirmed cases in March 2020. These issues may contribute to the increased number of asymptomatic cases in Indonesia. Also, despite the country borders limitation for travelers from the infectious area and thermal scan for passengers in the airport especially those from mainland China, the positive cases keep rising and early establishment of some local transmission area by authorities suggest many undetected positive cases. Although asymptomatic numbers were not officially announced by the government, several regional authorities in Indonesia expressed concern in the national media regarding the number of asymptomatic (National newspaper was access on 29 April 2020, http://jawapos.com).

Table 1. Summary of Asymptomatic COVID-19 Cases

Author	Study Location	N	Prevalence, n (%)	Gender (M/F)	Age	Tracing	Tier [f]	Travel history	Incubation length
Kong et al. (2020)[7]	Korea	28	3 (10,7%)	NA	NA	C, S	1; 2	+	4,1 day
Wei et al. (2020)[9]	Wuhan/ China	9	1 (11,1%)*	F	8m	C	NA	NA	NA
Bai et al. (2020)[6]	Anyang/ China	6	1 (16,6%)*	F	20y	C	1	+	NA
Chan et al (2020)[13]	Shenzen/ China	6	1 (16,6%)*	M	10y	C	1	+	NA
Hu et al. (2020)[12]	Nanjing/ China	24	19 (79,1%[a])* 5 (20,8%)** (2 diabetes and hypertension; 2 smoker)	8 M 16 F	5-95y	CC, C	1; 2	+	8-17 day
Nishiura et al. (2020)[14]	Japan	8	5 (62,5%)	NA	NA	S	1	+	NA
Mizumoto & Chowel (2020) [15]	Yokohama/ Japan	634	328 (51,4%)* 91.9 (20,6%)*** 130.8 (39,9%)****	NA	NA	S	1	+	NA
Zou et al. (2020)[16]	Zhuhai, Guangdong / China	18	1 (5,5%)* 3 (16,6%)**	NA	NA	CC, C	1; 2[b]	+	NA
Luo et al.[8]	Anqing/ China	83	1 (1,2%)* 7 (8,4%)**	F* NA	-	CC, C	2[c]; 3[d]	-	5[c]-15[d] day
Wang et al. (2020)[10]	Ahenzhen/ China	55	55 (100%)*****	22 M 33 F	2-69y	CC, C	NA	+[e]	3-14 day
Kimball et al. (2020)[11]	Washington / America	23	3 (13%)* 10 (43,4%)**	NA	NA[g]	S	NA	-	7 day

*Asymptomatic; **Presymptomatic; ***Estimated of asymptomatic proportions assuming 5.5 days incubation; ****Estimated of asymptomatic proportions assuming 9.5 days incubation; ***** = The study design involved all asymptomatic patients at the time of examination; M = male; F = female; m = month; y = year; a = The study design only involved asymptomatic patients; CC = Close contacts, individuals who were exposed to the COVID-19 patient within 2 meters for more than 1 hour within 2 days before the symptom onset of the patient; C = Cluster, cohabiting family members of the COVID-19 patient or suspected patient; S = Screening; b = Asymptomatic and presymptomatic cases come from tier 2 contacts; c = Tier 2 patients who contact Tier 1 have an incubation period of 5 days; d = Tier 3 patients who are in contact with Tier 2 have an incubation period of 15 days and have an asymptomatic partner; e = native Hubei resident; f = tier 1 (primary cases/import cases), tier 2 (secondary contact from primary cases/import cases), tier 3 (secondary contact from tier 2); g = geriatric population; NA = Non Available.

TWO ASYMPTOMATIC FACES: THE POTENTIAL FOR NEGLECTED DANGER

One of the asymptomatic conditions is pre-symptomatic, in which symptoms appeared shortly after the medical examination and correlates with the incubation period of COVID-19. Diverse COVID-19 incubation periods have been reported from various studies, varied from 4.75 until 6.4 days. [17–19] However, with larger samples, a study reported a median incubation period from 3 days to 24 days.[20] In Indonesia, the recent incubation period for COVID-19 can be up to 14 days.[21] In addition to the viral factors, other factors such as viral inoculum dose, host vulnerability, and immune response can affect different incubation periods. Problems arise when an infected person is still in the pre-symptomatic or asymptomatic stage since that person managed to escape COVID-19 screening. Although there was still controversy at the start of the epidemic, several recent reports supported the fact that asymptomatic cases can transmit COVID-19 in the same manner as the symptomatic ones. The viral

load between asymptomatic cases and symptomatic cases could be used to demonstrate the potential to exhibit the same degree of transmission.[22] A study from Shanghai reported an 88-year-old man with limited mobility who was only exposed by family members who confirmed positive without symptoms but after two weeks developed COVID-19 symptoms.[23] Epidemiologically proven transmission has occurred during the incubation period worldwide. A similar study report one person visited Germany for a meeting and after four days he returned to China and COVID-19 symptoms appeared. His business partners in Germany began to show symptoms on the sixth day and they were tested positive for COVID-19 confirmed by PCR results. This indicates the infection appeared to have been transmitted during the incubation period.[24,25]

COVID-19 or SARS-CoV-2 infection compared with previously established coronaviruses has a higher degree of infection. During the incubation period up to the first few days, the symptoms begin to appear, the SARS-CoV-2 virus produces 3.2 times more infectious virus particles compared to SARS-CoV measured as 48 hpi ($p = 0.024$) which indicates a high viral load at respiratory secretions of COVID-19 patients.[26–29] This occurs due to the condition of a low degree of innate immune activation in SARS-CoV-2 infection, where the virus triggered IFN production but was not significant and only activated five out of thirteen pro-inflammatory mediators. Low levels of IFN and proinflammatory cytokines could be used to support massive viral replication early in the course of infection and make COVID-19 more infectious.[26]

ALLEGED ASYMPTOMATIC MECHANISM

Many factors could facilitate the development of asymptomatic conditions. Symptoms that arise in infectious diseases are such complex conditions involving many interactions between environmental, host, and agent factors. Initially, climate parameters such as humidity, temperature, rainfall, and wind velocity were considered to correlate with the COVID-19 outbreak. Various studies reported changes in temperature were associated with COVID-19 outbreak events, in which the increase in temperature is linked to a decrease in the transmission rate.[30,31] Indonesia is a tropical country having dry and rainy seasons and the first case of COVID-19 was officially announced in Indonesia during the rainy season. In line with several studies conducted in China and America, a study in Indonesia also reported temperature changes that correlated with the COVID-19 outbreak, although the correlation was weak ($r = 0.392$; $p < 0.01$).[32]

From the perspective of the host factor, asymptomatic conditions could be triggered by numerous factors including age, variation in angiotensin-converting enzyme 2 (ACE2) expression, variations in human leukocyte antigen (HLA), and other comorbidities. Based on table 1, asymptomatic cases are more common in older people, while pre-symptomatic cases are prone to young people. The elderly group has more reactive immune genes produced by the immune system but cannot function efficiently and adaptively due to decreased type I IFN function and naïve T-cells, also increase of aged T-cells. Therefore, elderly people can develop both asymptomatic or symptomatic clinical features that are atypical and at a higher risk of severe condition manifestation.[33,34,10] Meanwhile in younger patients, pre-symptomatic is more common with longer incubation periods (≥12 days) and only mild symptoms with faster recovery for symptomatic cases.[33,35,12] In Indonesia, life expectancy is predicted to be increased from 70.1 years in 2010-2015 to 72.2 years in the period 2030-2035. In 2019, the elderly population in Indonesia is 57 million people or around 10.3% (Projection on Indonesia Population, Ministry of Affairs and Spatial Planning/National Land Agency) but Healthy Age Life Expectancy (HALE) in Indonesia is only 62.1 year, which means there is eight years difference in unhealthy conditions, so the risk and vulnerability to COVID-19 are considerably high in Indonesia (National Demographic Information, National Population, and Family Planning Board).

In specific populations, genetic variability correlates with a higher risk of being infected with the SARS-CoV-2 virus. It is reported that in specified HLAs such as HLA-B*15:03, it has the highest ability in presenting SARS-CoV-2 peptides. On the contrary, in HLA-B*46:01 there was fewer predicted binding peptides for SARS-CoV-2, making it more susceptible to COVID-19.[36,37] Since ACE2 receptors are an important part of the pathogenesis of COVID-19 and genetic variations can also affect variations in ACE2 receptor expressions especially for the role of interaction between SARS-CoV-2 and host. Recent *in vitro* studies reported the correlation between ACE2 expressions and human susceptibility to COVID-19.[38,23] A study reported the South and East Asians, in different-sex groups and ethnicity, comprised high variability of ACE2 and transmembrane protease, serine 2 (TMPRSS2) expressions.[39] Additionally, unhealthy lifestyles like smoking can increase the risk of being infected with SARS-CoV-2 and it was linked to the upregulation of ACE2 in the respiratory tract epithelium of active smokers.[40–42] In 2016 the Southeast Asia Tobacco Control Alliance (SEATCA) reported that as many as 65.19 million Indonesians or 34% of the total population were active smokers. Based on this data, Indonesia has the highest number of smokers in ASEAN and considered as the most vulnerable population to COVID-19 (Statistics Indonesia, http://www.bps.go.id/).

Various factors in humans can affect the progress of COVID-19 infection, such as the correlation between the amount of virus being inoculated and the immune system condition during pre-symptomatic conditions (incubation period), genuine asymptomatic and pseudo-asymptomatic. As seen in other infectious diseases, COVID-19 infection also has an incubation period where the virus inoculation progressed until the symptoms emerged. This correlates with the timing of viral detection. Based on table 1, most asymptomatic patients were diagnosed through active tracking of having close contact with a previously infected patient. Genuine asymptomatic conditions can be caused by low virus

levels during the inoculation phase responded to the optimal immune response so the virus could be inactivated before causing any apparent symptoms. Although there has been no research on the correlation of the amount of virus during inoculation to variability in host immune response, incubation period, and symptoms at the onset of infection, several reports have compared viral load levels at the start of inoculation with symptoms. A low viral load at the onset of symptoms caused a mild clinical manifestation compared to a high viral load. It was concluded that a low viral load assisted the development of the asymptomatic case and extended viral incubation period.[12,16,10,43–46]

The second hypothesis predicted individuals in immunocompromised groups such as diabetes[47,48] or autoimmune[49,50] patients showed delayed detection in the immune system when COVID-19 infection occurred and poor prognosis later on. To date, there are 10 million diabetic patients in Indonesia (approximately 6.2% of the total population) causing Indonesia ranked the fourth-highest country with diabetic cases globally after India, China, and the United States. The number is expected to increase to 21.3 million in 2030 (Basic Health Research 2018, Ministry of Health, http://www.kesmas.kemkes.go.id/; International Diabetes Federation (IDF), https://idf.org/our-network/regions-members/western pacific/members/104-indonesia).[51] Although data on the exact number of autoimmune diseases in Indonesia is relatively unknown, it is suspected that 1.2 million people in Indonesia suffer from autoimmune diseases (Data and Information Center 2017, Ministry of Health, http//www.perdatin.kemkes.go.id/). Most cases of COVID-19 infections have mild clinical symptoms or asymptomatic, and in some cases, the symptoms reported are not typical, and because of the perception of symptom cannot be separated from subjective elements, in pseudo-asymptomatic cases with mild symptoms, patients tend to ignore such minor discomforts and to make it worse they tend to deny or hide it.

From the point of view as an agent factor, the SARS-CoV-2 virus has different mechanisms to escape the host immune system that can affect the incidence and severity of symptoms and the subsequent risk of transmission. The pathogenesis of SARS-CoV-2 is not fully known yet, but compared to coronavirus families, SARS-CoV has similar nucleotide sequences and unique structure resulting in new variants of protein structures in envelopes and nucleocapsids, with 96% and 89.6% similarities, respectively.[17] The major transmission route is a direct contact facilitated by water droplets originating from talking, coughing, and sneezing from an infected person. The virus inside the droplets can survive in the open air temporarily before finally settling on the object's surface. Subsequently those virus particles can enter the new host through the eyes, nose, and mouth as the start of a new transmission. Before causing the actual symptoms, the SARS-CoV-2 initially triggers an innate and adaptive immune response. Innate immunity comprises of anatomical, cell, and humeral barrier, while adaptive immunity works through T and B-lymphocytes. Upon entering the host through one of the viral structure antigens, namely the S antigen, the virus can bind to the angiotensin-converting enzyme-2 receptor (ACE-2) contained in various cells, especially airway epithelial cells, namely pneumocytes type II in the lungs, enterocytes, and in some immune cells such as macrophages, T cells, and later on this whole process will trigger an inflammatory cascade to be activated.[5,13,18,40,52,53] After the S antigen binds to ACE-2, TMPRSS2, which is a type 2 transmembrane protease, breaks down ACE-2 and activates the S protein, which then stimulates the entry of the virus into the cell.[20,21]

The innate immune system can identify the virus structure, dsRNAs as pathogen-associated molecular patterns (PAMPs) that directly will be recognized by pattern recognition receptors (PRRs) 6, including endosome receptors, namely Toll-like receptors (TLRs), Retinoid-inducible gene (RIG), and melanoma differentiation-associated gene 5 (MDA5).[22,25,24] Upon recognition, signaling pathways, and transcription factors such as nuclear factor κB (NF-κB), activator protein-1 (AP-1), interferon response factor 3 (IRF3) and IRF 7 are fully activated. NF-κB and AP-1 will trigger gene expression of various pro-inflammatory molecules such as tumor necrotizing factor α (TNF-α), interleukin-1 (IL-1), and chemokines.[26] Besides, IRF3, IRF7, and NF-κB interact with nuclear translocation to initiate the production of type I interferons (IFN-I) that play a role in the innate immune system by controlling viral replication especially in the early phases of the disease.[25,27,28] IFN type I through IFNAR activates the JAK-STAT pathway facilitated by JAK1 and TYK2 kinases phosphorylate and also STAT1 and STAT2. The STATs formed a complex with IRF9 and enter the nucleus to begin transcription of IFN-stimulated genes (ISGs). [26,24]

The incubation period of COVID-19 is directly dependent on the ability of the SARS-CoV virus to perform various mechanisms to escape the immune system (as summarized in Figure 2), firstly by inducing double-membrane vesicles that lack PRRs.[24,29] Secondly, through the transmembrane protein ORF7a, SARS-CoV can also inhibit bone marrow stromal antigen 2 (BST2), a component of the innate immune response responsible in conducting restricted enveloped virion release by interfering with glycosylation from BST2.[54] One component that plays an important role in innate immune system in controlling viral replication is IFN type I.[55,56] However, SARS-CoV virus can also inhibit IFN type I inhibition through immobilization of IRF-3 from the nucleus to the cytoplasm to create a type I IFN barrier especially IFN-β.[57–60] SARS-CoV also inhibits activation of IRF7 as reported upon 48 hours after infection, no IFN type I detected in patients infected with SARS-CoV.[26] The other mechanism involves a direct interference with STAT1 activation to blocking the induction of IFN.[61,62]

Endocytosis at the ACE-2 receptor activated the host immune response and the inflammatory cascade through antigen-presenting cells (APC). Afterward, APC presented virus isotope to CD4+ T-helper (Th1) cells via

major histocompatibility complex (MHC) class II and produced interleukin-12 (IL-12) that activated Th1 via interferon-γ (IFN-γ).[63] Th1 stimulated CD8+ T cells via IL-2 to eradicate intracellular viruses and also to stimulate B cells for specific antibodies development. These antibodies controlled the virus in the humoral pathway, before entering the cell. Specific antibodies for immunoglobulin M (IgM) will be produced within 5 days (IQR 3-6 days) after onset and reach the peak after day 7. Meanwhile, IgG is developed approximately 14 days (IQR 10-18 days) after symptoms arising.[25,64,65]

In mid-March 2020, the Indonesian government imported rapid test kits to detect both IgM/IgG antibodies of COVID-19 as a screening guideline.[66] This was done to support the COVID-19 massive-scale testing program recommended by WHO, although this step might backfire since the results could be unreliable. Since IgM antibodies only reached its peak after 5 days, then this rapid test examination can only help when the suspects got checked after 5 days upon transmission. For such a case when a suspect is examined before day 5, there might be misleading false-negative results, as the immune system has not yet produced the targeted antibodies. However, the Indonesian government proceeds to confirm the rapid test results by the RT-PCR method. A study reported diverse results for sensitivity and specificity of antibodies-based rapid as 88.66% and 90.63%, respectively.[64] However, other studies referred to the numbers as 18.4% for sensitivity and 91.7% for specificity.[66] Those variables might cause many false-negative results for COVID-19 detection in Indonesia, and further studies are needed to create more reliable rapid test kits.

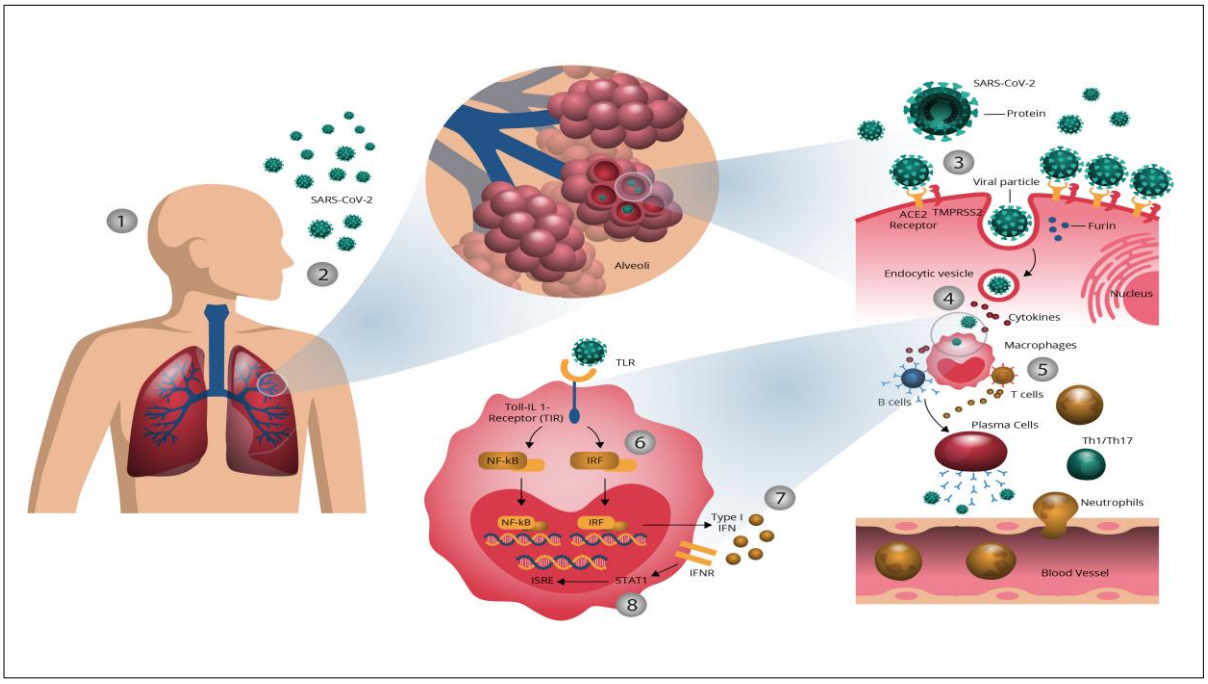


Figure 2. Asymptomatic cases mechanism. 1. Age; 2. Viral dose inoculation; 3. ACE2 variability expression; 4. Double-membrane vesicle; 5. HLA variability; 6. IRF inactivation; 7. Impaired Type I IFN function and production; 8. Impaired STAT1 function

SCREENING AND MANAGEMENT ISSUES IN ASYMPTOMATIC CASES

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. One step in managing infectious diseases is to control direct transmission. One parameter to assess COVID-19 transmission is the basic reproductive number (R0), which is the addition of some new developed cases resulting from previous positive cases. R0 value is usually used to describe the potential and severity of an infectious disease. The greater value of R0 represents higher transmission rates in humans. Compared to the R0 of MERS-CoV (<1-5.7) and SARS-CoV (2.2-3.6), SARS-CoV-2 reproductive number is relatively low, which is 2.2-2.68, indicating a limited transmission potential.[12,21] However, R0 can be influenced by several factors such as host[67–69], environmental[30,31], and agent factors[57–60]. The combination of these three factors can also affect the clinical spectrum of individuals infected with COVID-19. The rapid increase of COVID-19 cases in Indonesia is associated with population susceptibility and SARS-CoV2 mutation rates.[70]

Best-practice of handling COVID-19 in various countries in the world is limiting the transmission through suppression and mitigation approaches. In terms of suppression, the massive scale screening and history tracing followed by self-isolation is the best tactic. Both of those approaches seem to like racing against time as the COVID-19 cases increased rapidly over a short time. The more detected cases published and immediate contact tracing applied, the government seemed to be in

an irrational fight against the rapid transmission of COVID-19. The effectiveness of self-isolation and contact tracing to prevent transmission by COVID-19 patients was reported in a research model, in 2.5 reproductive numbers to be able to control 90% of outbreaks, 80% of suspects must be tracked and isolated.[71] The probability of this approach of disease control succeeded will be increased if the reproductive number gets smaller.[71] Conversely, the probability will decrease if there is a prolongation between the onsets of symptoms with the time of isolation. It was reported that if 80% of suspects had been traced, the probability will decrease from 89% to 31%.[71] The delayed onsets of COVID-19 symptoms as seen in asymptomatic or a pre-symptomatic case is linked to long viral incubation period and long interval in isolating symptomatic suspects.[30]

However, various aspects occurring in Indonesia can become obstacles in managing the COVID-19 outbreak. The biggest challenge is the total population of Indonesia is 269.6 million people (Statistics Indonesia, http://www/bps.go.id/), spread over 2.01 million km^2, and 16,056 islands in Indonesia. The majority of 124, 27 million (46%) people are located in Java Island with a coverage area of 128,297 km^2. This resulted in a high population density level of 1.317/ km^2 inhabitants where most of them located in the three big cities in Java. Jakarta as a capital city of Indonesia, with an area of 661.5 km^2 having a population of 10.5 million people followed by Bandung with an area of 167.7 km^2 has a population of 2.5 million people. Additionally, Surabaya with an area of 350.5 km^2 has a population of 2.89 million people (Statistics Indonesia, http://www/bps.go.id/). This high population density might facilitate the rapid transmission of COVID-19 in those large cities. Another challenge is the majority of Jakarta residents' high mobility rates, thus limiting their movements for social distancing, and self-isolation during the outbreak is becoming a high priority according to recent government regulations. Also, as Indonesia is the biggest Muslim country, the homecoming customs during Eid al-Fitr might cause a second outbreak wave as people travel within the country to visit their family and relatives.

At the beginning of the COVID-19 outbreak, the asymptomatic cases were ruled out because initially it was briefed in WHO official statement that they covered small percentages of total COVID-19 cases and the transmission is fairly limited, although later on that statement was corrected.[72] By April 2020, WHO also stated there was no supportive evidence in wearing masks for healthy people could prevent direct transmission of COVID-19.[73] However, with some reports of transmission via asymptomatic cases and several reports and meta-analyses stating the protective role of masks in all community groups, the Indonesian government changed its policy to suggest all citizens wearing protective masks (Self-isolation National Protocol). [74–77]

Case finding on symptomatic and asymptomatic plays a critical role in COVID-19 management, the better capability of a country to conduct an early detection, the more number of asymptomatic cases are traced. Thus, the proportion of asymptomatic cases reflects the screening coverage ability of a country. Nevertheless, asymptomatic cases are also affected by the incubation period by means it depends on the host side. Approximately, the viral incubation period lasted for 5 days, this suggested that early detection is a must to identify the asymptomatic cases and to prevent the higher transmission rate in each country. As seen in China, the majority of confirmed cases originated from tracking isolated suspects and suspected population are determined by the detection rate and detection ratio of each group.[78]

As for Indonesia, the limitation of surveillance facilities, mainly performed by 9,993 Community Health Center (Puskesmas in Indonesia) was not enough for COVID-19 management. Ideally, the ratio of 1.39 per sub-district for Puskesmas is needed with a minimum of one puskesmas per sub-district. However, only Jakarta and Bali could achieve that, whereas Papua and West Papua have the lowest ratios of 0.73 Puskesmas per district (Indonesian Health Profile, Ministry of Health, http://www.kemkes.go.id/). This directly correlated with the ability of the local community to gain access to primary health services. The primary health accessibility is also influenced by various factors including geographical conditions, area size, availability of basic facilities and infrastructure, and social economics. The ratio of health facilities in Indonesia compared to its population is 1.17:1000, far from ideal as recommended by WHO, which is 5:1000 (Indonesian Health Profile, Ministry of Health, http://www.kemkes.go.id/). The Indonesian government decided not to do active tracing for the COVID-19 suspects, but instead using passive tracing mechanism, by combining social measures with limiting massive-scales mobility and actual reports from the COVID-19 positive cases, although those acts were only accessible by the relevant authorities. The number of laboratories that can conduct RT-PCR examinations is also limited, a total of only 46 centers in Indonesia (Ministry of Health, data obtained 29 April 2020, http://www.litbang.kemkes.go.id/). With such limited sources, Indonesia can only do 526 tests per 1 million population, lower than the neighboring countries such as Vietnam with 2623 tests per 1 million population, Thailand 3264 tests per 1 million population, and Malaysia 7573 tests per 1 million population (Live coronavirus statistics, https://www.worldometers.info/coronavirus/).
Additionally, reporting procedures and confirmation of examination results are also complicated in Indonesia. Based on the guidelines from WHO, the Chinese CDC, American CDC, the results of the RT-PCR examination in unnecessarily followed by sequencing, while the regulation from the Ministry of Health in Indonesia stated that all positive RT-PCR cases have to be sent to National Research and Development Center for DNA sequencing. This regulation created a delay in delivering the RT-PCR results to the suspects since it will take days to wait for DNA sequencing results, instead of 24 hours waiting period for RT-PCR result only. To date, the Indonesian government realized that the sequencing procedure would only slow down the COVID-19 mass

detection so that in the 4th national guidance of COVID-19 management the sequencing procedure was eradicated (Ministry of Health, 3rd and 4th edition of National Guidelines for COVID-19 Prevention and Control). Due to the limited healthcare facilities, the Indonesian government only issued recommendation letters, to be admitted to the COVID-19 designated hospitals, to the symptomatic individuals and the suspects who are considered at high risk of infection, rather than to instruct mass COVID-19 screening.

Based on WHO official statements, COVID-19 suspects are screened according to the following symptoms namely fever, cough, runny nose, spasms, and a history of contact or travel to a country with high COVID-19 cases. Indirectly, this regulation causes asymptomatic cases to be invisible and remains undetected. A study analyzing the effectiveness of these criteria stated that symptoms screening could only detect less than half of COVID-19 cases is rapidly growing epidemic conditions. The two major causes revealed, firstly screening apparent symptoms are very dependent on the natural history of infection that will be difficult to assess when the incubation period is varied. The problem becomes more complicated during the longer incubation period since the incubation period of the SARS-CoV-2 virus is expected to be happening within 2-14 days.[1,46] Secondly, some individuals with early COVID-19 symptoms are healthy enough to carry out their daily activities; hence they might avoid getting tested.

In Indonesia, those conditions are worsened by several other factors. The major apparent case is patient dishonesty in presenting exposure risk data that can cause false statements and reduce effectiveness in screening history of COVID-19 exposure. Aside from causing transmission problems in the local community, this dishonesty problem created big chaos to COVID-19 treatment centers in Indonesia. Besides, Indonesia is a tropical country that has other endemic infections, namely typhoid fever, malaria, dengue fever, measle, and others. Upon the COVID-19 outbreak, Indonesia has been experiencing the rainy season causing the increased cases of other seasonal related infectious diseases such as dengue fever and influenza infections. Those seasonal infections have similar symptoms as COVID-19 especially the fever manifestations causing the overcapacity at the emergency ward. The WHO guidelines adopted by the Indonesian government in COVID-19 detection are by the use of RT-PCR, but during the process the examinations must be centrally re-confirmed, resulting in a delayed diagnosis of COVID-19 patients up to an average of 5 days. More problems arose, as during 5 days waiting period of RT-PCR results, the patient should have been isolated or if his/her symptoms get worsened must be immediately being treated at the designated hospital. However, since the RT-PCR has not been confirmed yet, possibly the patient got admitted to the hospital without proper measurements causing alarming risks for all the medical staff without proper personal protective equipment. Consequently, large numbers of medical staff got infected by COVID-19, transmitted by those unidentified patients.[79]

CONCLUSION

SARS-CoV-2 is the cause of the recent pandemic worldwide named as COVID-19. This viral infection can affect all ages with all clinical conditions. Clinical manifestations can be varied from asymptomatic, mild, moderate, severe to respiratory failure. Currently, most studies focused only on severe cases of COVID-19 and the following mortality whereas in asymptomatic cases tend to be underestimated because the outcome is unclear. However, the absence of the symptoms combined with the ongoing transmission rate becomes a challenge in the management of COVID-19 transmission. This can also be a major threat in Indonesia, considering Indonesia is the fourth largest country in the world, and if Indonesia is unable to handle and manage COVID-19, there will be a massive contamination rate with high morbidity and mortality. A comprehensive understanding of the characteristic of asymptomatic cases in COVID-19 can help the government to conceive better policies to control this pandemic.

ACKNOWLEDGMENTS

This study was funded by grants from the Riset Mandat 2019 Grant from Universitas Airlangga (340/ UN3.14/LT/2019).

REFERENCES

1. World Health Organization (WHO). Novel Coronavirus (2019-nCoV) Situation Report - 1 21 January 2020. WHO Bull. 2020;(JANUARY):1–7.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb;395(10223):497–506.
3. Wu Y-C, Chen C-S, Chan Y-J. The outbreak of COVID-19. J Chinese Med Assoc. 2020;83(3):217–20.
4. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol. 2020 Mar;
5. WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020;2019(March).
6. Bai Y, Yao L, Wei T, Tian F, Jin DY, Chen L, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. Vol. 323, JAMA - Journal of the American Medical Association. American Medical Association; 2020. p. 1406–7.
7. Kong I, Park Y, Woo Y, Lee J, Cha J, Choi J, et al. Early epidemiological and clinical characteristics of 28 cases of coronavirus disease in South Korea. Osong Public Heal Res Perspect. 2020;11(1):8–14.
8. Luo SH, Liu W, Liu ZJ, Zheng XY, Hong CX, Liu ZR, et al. A confirmed asymptomatic carrier of 2019 novel coronavirus (SARS-CoV-2). Chin Med J (Engl). 2020;
9. Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel Coronavirus Infection in Hospitalized Infants under 1 Year of Age in China. Vol. 323, JAMA - Journal of the American Medical Association. American Medical

Association; 2020. p. 1313–4.
10. Wang Y, Liu Y, Liu L, Wang X, Luo N, Ling L. Clinical outcome of 55 asymptomatic cases at the time of hospital admission infected with SARS-Coronavirus-2 in Shenzhen, China. J Infect Dis. 2020;2:1–5.
11. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Asymptomatic and presymptomatic SARS-COV-2 infections in residents of a long-term care skilled nursing facility - King County, Washington, March 2020. Vol. 69, Morbidity and Mortality Weekly Report. Department of Health and Human Services; 2020. p. 377–81.
12. Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020;
13. Chan JFW, Yuan S, Kok KH, To KKW, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020 Feb;395(10223):514–23.
14. Nishiura H, Kobayashi T, Yang Y, Hayashi K, Miyama T, Kinoshita R, et al. The Rate of Underascertainment of Novel Coronavirus (2019-nCoV) Infection: Estimation Using Japanese Passengers Data on Evacuation Flights. J Clin Med. 2020;9(2):419.
15. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020;25(10):1–5.
16. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. Vol. 382, New England Journal of Medicine. Massachussetts Medical Society; 2020. p. 1177–9.
17. Liu YC, Liao CH, Chang CF, Chou CC, Lin YR. A locally transmitted case of SARS-CoV-2 infection in Taiwan. Vol. 382, New England Journal of Medicine. Massachussetts Medical Society; 2020. p. 1070–2.
18. Cameron MJ, Ran L, Xu L, Danesh A, Bermejo-Martin JF, Cameron CM, et al. Interferon-Mediated Immunopathological Events Are Associated with Atypical Innate and Adaptive Immune Responses in Patients with Severe Acute Respiratory Syndrome. J Virol. 2007 Aug;81(16):8692–706.
19. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005 Aug;11(8):875–9.
20. Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O, Pohlmann S. TMPRSS2 and ADAM17 Cleave ACE2 Differentially and Only Proteolysis by TMPRSS2 Augments Entry Driven by the Severe Acute Respiratory Syndrome Coronavirus Spike Protein. J Virol. 2014 Jan;88(2):1293–307.
21. Glowacka I, Bertram S, Muller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 Activates the Severe Acute Respiratory Syndrome Coronavirus Spike Protein for Membrane Fusion and Reduces Viral Control by the Humoral Immune Response. J Virol. 2011 May;85(9):4122–34.
22. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol. 2020;92(4):424–32.
23. Yu P, Zhu J, Zhang Z, Han Y, Huang L, Luchicchi A, et al. A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. J Infect Dis. 2020;
24. De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: Recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–34.
25. Rokni M, Ghasemi V, Tavakoli Z. Immune responses and pathogenesis of SARS-CoV-2 during an outbreak in Iran: Comparison with SARS and MERS. Rev Med Virol. 2020;(March):1–6.
26. Yoshikawa T, Hill TE, Yoshikawa N, Popov VL, Galindo CL, Garner HR, et al. Dynamic innate immune responses of human bronchial epithelial cells to severe acute respiratory syndrome-associated coronavirus infection. PLoS One. 2010 Jan;5(1).
27. Yang CH, Li K, Pfeffer SR, Pfeffer LM. The type I IFN-Induced miRNA, miR-21. Vol. 8, Pharmaceuticals. MDPI AG; 2015. p. 836–47.
28. Okabe Y, Kawane K, Nagata S. IFN regulatory factor (IRF) 3/7-dependent and -independent gene induction by mammalian DNA that escapes degradation. Eur J Immunol. 2008;38(11):3150–8.
29. Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, Onderwater JJM, van der Meulen J, Koerten HK, et al. Ultrastructure and Origin of Membrane Vesicles Associated with the Severe Acute Respiratory Syndrome Coronavirus Replication Complex. J Virol. 2006 Jun;80(12):5927–40.
30. Bashir MF, Ma B, Bilal, Komal B, Bashir MA, Tan D, et al. Correlation between climate indicators and COVID-19 pandemic in New York, USA. Sci Total Environ. 2020;
31. Shi P, Dong Y, Yan H, Zhao C, Li X, Liu W, et al. Impact of temperature on the dynamics of the COVID-19 outbreak in China. Sci Total Environ. 2020;
32. Tosepu R, Gunawan J, Effendy DS, Ahmad LOAI, Lestari H, Bahar H, et al. Correlation between weather and Covid-19 pandemic in Jakarta, Indonesia. Sci Total Environ. 2020 Jul;725.
33. Baas T, Roberts A, Teal TH, Vogel L, Chen J, Tumpey TM, et al. Genomic analysis reveals age-dependent innate immune responses to severe acute respiratory syndrome coronavirus. J Virol. 2008 Oct;82(19):9465–76.
34. Oh SJ, Lee JK, Shin OS. Aging and the immune system: The impact of immunosenescence on viral infection, immunity and vaccine immunogenicity. Immune Netw. 2019 Dec;19(6).
35. Subbarao K, McAuliffe J, Vogel L, Fahle G, Fischer S, Tatti K, et al. Prior Infection and Passive Transfer of Neutralizing Antibody Prevent Replication of Severe Acute Respiratory Syndrome Coronavirus in the Respiratory Tract of Mice. J Virol. 2004 Apr;78(7):3572–7.
36. Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, et al. Human leukocyte antigen

susceptibility map for SARS-CoV-2. J Virol. 2020;(April).
37. Chen YMA, Liang SY, Shih YP, Chen CY, Lee YM, Chang L, et al. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. J Clin Microbiol. 2006;
38. Qian Z, Travanty EA, Oko L, Edeen K, Berglund A, Wang J, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus. Am J Respir Cell Mol Biol. 2013 Jun;48(6):742–8.
39. Ortiz-Fernández L, Sawalha AH. Genetic variability in the expression of the SARS-CoV-2 host cell entry factors across populations. bioRxiv. 2020 Apr;2020.04.06.027698.
40. Zhao, Y.; Zhao, Z.; Wang, Y.; Zhou, Y.; Ma, Y.; Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. bioRxiv. 2020;bioRxiv:20.
41. Wang, J.; Lou, Q.; Chen, R.; Chen, T.; Li J. Susceptibility Analysis of COVID-19 in Smokers Based on ACE2. Preprints. 2020;
42. Brake SJ, Barnsley K, Lu W, Mcalinden KD, Eapen MS, Sohal SS. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor : A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). 2020;
43. Kim JY, Ko JH, Kim Y, Kim YJ, Kim JM, Chung YS, et al. Viral load kinetics of SARS-CoV-2 infection in first two patients in Korea. J Korean Med Sci. 2020 Feb;35(7).
44. Chu CM, Poon LLM, Cheng VCC, Chan KS, Hung IFN, Wong MML, et al. Initial viral load and the outcomes of SARS. CMAJ. 2004 Nov;171(11):1349–52.
45. Xu T, Chen C, Zhu Z, Cui M, Chen C, Dai H, et al. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. Int J Infect Dis. 2020 May;94:68–71.
46. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-NCOV infection from an asymptomatic contact in Germany. Vol. 382, New England Journal of Medicine. Massachussetts Medical Society; 2020. p. 970–1.
47. Hu R, Xia CQ, Butfiloski E, Clare-Salzler M. Effect of high glucose on cytokine production by human peripheral blood immune cells and type I interferon signaling in monocytes: Implications for the role of hyperglycemia in the diabetes inflammatory process and host defense against infection. Clin Immunol. 2018 Oct;195:139–48.
48. Del Rio C, Malani PN. COVID-19 - New Insights on a Rapidly Changing Epidemic. Vol. 323, JAMA - Journal of the American Medical Association. American Medical Association; 2020. p. 1339–40.
49. Crow MK. Type I Interferon in the Pathogenesis of Lupus. J Immunol. 2014;
50. Muskardin TLW, Niewold TB. Type i interferon in rheumatic diseases. Vol. 14, Nature Reviews Rheumatology. Nature Publishing Group; 2018. p. 214–28.
51. WHO Library. Global Report on Diabetes. Isbn [Internet]. 2016;978:6–86. Available from: http://www.who.int/about/licensing/
52. Kuba, K.; Imai, Y.; Rao, S.; Gao, H.; Guo, F.; Guan, B.; Huan, Y.; Yang, P.; Zhang, Y.; Deng W. et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med. 2005;11:875–9.
53. Coutard, B.; Valle, C.; de Lamballerie, X.; Canard, B.; Seidah, N.G.; Decroly E. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antivir Res. 2020;176(104742).
54. Wang SM, Huang KJ, Wang CT. Severe acute respiratory syndrome coronavirus spike protein counteracts BST2-mediated restriction of virus-like particle release. J Med Virol. 2019;
55. Lokugamage KG, Hage A, Schindewolf C, Rajsbaum R, Menachery VD. SARS-CoV-2 is sensitive to type I interferon pretreatment. bioRxiv. 2020;
56. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. Lancet. 2003;
57. Spiegel M, Pichlmair A, Martínez-Sobrido L, Cros J, García-Sastre A, Haller O, et al. Inhibition of Beta Interferon Induction by Severe Acute Respiratory Syndrome Coronavirus Suggests a Two-Step Model for Activation of Interferon Regulatory Factor 3. J Virol. 2005;
58. Kuri T, Zhang X, Habjan M, Martínez-Sobrido L, García-Sastre A, Yuan Z, et al. Interferon priming enables cells to partially overturn the SARS coronavirus-induced block in innate immune activation. J Gen Virol. 2009;
59. Matthews K, Schäfer A, Pham A, Frieman M. The SARS coronavirus papain like protease can inhibit IRF3 at a post activation step that requires deubiquitination activity. Virol J. 2014;
60. de Lang A, Geurts van Kessel CH, Osterhaus ADM., Haagmans BL. Interferon response in murine plasmacytoid dendritic cells after SARS coronavirus infection. Cytokine. 2009;
61. Frieman M, Yount B, Heise M, Kopecky-Bromberg SA, Palese P, Baric RS. Severe Acute Respiratory Syndrome Coronavirus ORF6 Antagonizes STAT1 Function by Sequestering Nuclear Import Factors on the Rough Endoplasmic Reticulum/Golgi Membrane. J Virol. 2007 Sep;81(18):9812–24.
62. Page C, Goicochea L, Matthews K, Zhang Y, Klover P, Holtzman MJ, et al. Induction of Alternatively Activated Macrophages Enhances Pathogenesis during Severe Acute Respiratory Syndrome Coronavirus Infection. J Virol. 2012;
63. Mosaddeghi P, Negahdaripour M, Farahmandnejad M, Taghipour MJ, Moghadami M, Nezafat N, et al. Therapeutic approaches for COVID-19 based on the dynamics of interferon- mediated immune responses. Preprints. 2020 Mar;(March):2020030206.
64. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020;

65. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clin Infect Dis. 2020;
66. Cassaniti I, Novazzi F, Giardina F, Salinaro F, Sachs M, Perlini S, et al. Performance of VivaDiag COVID-19 IgM/IgG Rapid Test is inadequate for diagnosis of COVID-19 in acute patients referring to emergency room department. J Med Virol. 2020;1–4.
67. Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: A Nationwide Analysis. Eur Respir J [Internet]. 2020; Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L631357733%0Ahttp://dx.doi.org/10.1183/13993003.00547-2020
68. Beck MA, Levander OA. Host Nutritional Status and Its Effect on a Viral Pathogen. J Infect Dis. 2000;182(s1):S93–6.
69. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: A systematic review. J Med Virol. 2020;92(5):479–90.
70. World Health Organization (WHO). Media statement: Knowing the risks for COVID-19. 2020;
71. Hellewell J, Abbott S, Gimma A, Bosse NI, Jarvis CI, Russell TW, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. Lancet Glob Heal. 2020;8(4):e488–96.
72. Bruce Aylward (WHO); Wannian Liang (PRC). Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). WHO-China Jt Mission Coronavirus Dis 2019 [Internet]. 2020;1(February):40. Available from: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
73. Organization WH. Advice on the use of masks in the context of COVID-19: interim guidance, 6 April 2020. Geneva PP - Geneva: World Health Organization;
74. Cheng VCC, Wong S-C, Chuang VWM, So SYC, Chen JHK, Sridhar S, et al. The role of community-wide wearing of face mask for control of coronavirus disease 2019 (COVID-19) epidemic due to SARS-CoV-2. J Infect. 2020 Apr;
75. Javid B, Balaban NQ. Impact of population mask wearing on Covid-19 post lockdown. medRxiv. 2020 Apr;2020.04.13.20063529.
76. Liang M, Gao L, Cheng C, Zhou Q, Uy JP, Heiner K, et al. Efficacy of face mask in preventing respiratory virus transmission: a systematic review and meta-analysis. medRxiv. 2020 May;2020.04.03.20051649.
77. Eikenberry SE, Mancuso M, Iboi E, Phan T, Eikenberry K, Kuang Y, et al. To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. Infect Dis Model. 2020 Jan;5:293–308.
78. Sanyi T, Yanni X, Zhixing P. Prediction modeling , data fusion and prevention and control strategy analysis of new coronavirus pneumonia. 2020;1–7.
79. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation Report 82. Coronavirus Dis 2019 [Internet]. 2020;2019(April):2633. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019