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Original Research Article

COVID-19 Pandemic: Factors Contributing to Persistent Infection and Severe Cases

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Abstract

Presently it is an era of viral foes against humanity. No one could expect the breakout of a new viral epidemic unless we make efforts to investigate new viruses in the wildlife and wet meats of exotic animals. Despite the prolonged duration of lockdown to control the transmission and the recovery of infected patients with SARS-CoV-2 virus, there are many new cases and deaths. Reviewing the literature provides the rationale behind daily reported new cases and deaths. Incomplete clearance of the virus new mutated genomic variants or a lack of immunisation against the virus could lead to re-infection or persistent infection. The severity of COVID-19 could be due to co-infection with other pathogens, chronic infections, nosocomial infections, highly virulent variants of the virus, or highly upregulated angiotensin-renin converting enzyme receptors II (ACE-II) in patients who have a history of hypertension, chronic chest infections or diabetes. Even after the lockdown is over, we should maintain good personal hygiene, physical distancing, wear face mask and gloves. Developing a safe and effective vaccine and antiviral agents could control the transmission and epidemic of SARS-CoV-2 virus.

Keywords: COVID-19, Pandemic, COVID-19, Infection, Severe cases

Introduction

Human infectious diseases are communicable diseases that can spread directly or indirectly from a human to another. They are caused by pathogenic microorganisms including bacteria, fungi, viruses and parasites [1]. Some infectious diseases are emerging because they are newly appeared in the population, and the number of cases increases rapidly [2]. A super-spreading event is a phenomenon in the inter-individual transmission of infectious diseases due to changes in transmission dynamics attributed by co-infection with another pathogen, immune suppression, changes in airflow dynamics, delayed in hospital admission, misdiagnosis, and inter-hospital transfers [3].

Viral infections are the most common human infectious diseases in which the severity ranging from life-threatening to mild, self-limiting or asymptomatic. These infection s are characterised by rapid transmission and morbidity [4]. The emerging pandemic viral infections constitute a constant threat to communities. They are transmitted from human to another human or from animal to human, similar toSARS-CoV-1 (severe acute respiratory syndrome), MERS-Cov (Middle East respiratory syndrome), Ebola and Zika viruses [5].

On 12 December 2019, coronavirus disease-2019 (COVID-19) starts as an epidemic in the city of Wuhan in China [6] and then spread worldwide [7]. On 31 December 2019, the Chinese Country Office of the World Health Organization (WHO) was informed of cases of pneumonia of unknown a etiology detected in Wuhan City, Hubei Province of China, and then WHO reported a new coronavirus, called 2019-nCoV, which was identified on 7January 2020 by the Chinese authorities as to the causative virus of Wuhan pneumonia. On 11 February 2020, International Committee on Taxonomy of Viruses named 2019-nCoV as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [8].

There have been still new cases of infection and deaths with no sign to slow down [9]. Up to 23August 2020, the newly emerging virus (SARS-CoV-2) outbreaks all over the world and affected 23,057,288 confirmed cases of which 800,906 harvested deaths [10]. Nonetheless, the outbreak of SARS-CoV-2 virus among humans has been still not well controlled and constituted a global health burden in terms of morbidity, comorbidity and mortality. The mortality rate of COVID-19depends on age, smoking habit, comorbidity, country and region [11]. Although prolonged lockdown everywhere, there are still new cases reported every day. Therefore, the former issue hypothesises several reasons that stand behind the new cases of infection and deaths including either dynamics of SARS-CoV-2 transmission, misleading diagnosis, re-infection with the virus in the recovered COVID-19 patients, missed preventive and treatment measures. Accordingly, this narrative review focused on debatingthe reasons that stand behind the incidence of new cases of infection and deaths due to severity of COVID-19 during the prolonged duration of lockdown everywhere depending on the published studies, preprints, reports and guidelines available in the scientific literature and publicly online sources. The goal of this

article is to provide an overview of COVID-19 and the outbreak of COVID-19 virus among humans has been still not well controlled.

Discussion

Nomenclature and sources of SARS-CoV-2

After SRAS-CoV-2 was identified as the causative virus of COVID-19, the WHO began to look for the source of the virus to avoid transmission. Earlier in October 2019, Liu, Chen 12 reported that Malayan Pangolins (Manis javanica) is a host of a potential several pathogenic coronaviruses SARS-CoV, which gave rise to the earlier prediction of viral zoonosis epidemics to become a major public health issue since the meat and scales of Pangolin is highly required by the people of some Asian countries either for delicacy or traditional medicine use, respectively 12. In 2020, It has been reported that Pangolin-CoV is 91.02% and 90.55% identical to SARS-CoV-2 and BatCoV RaTG13 at the whole genome level 7. On the other hand, another source of SARS-CoV-2 was reported to be bat origin, while virus might be transmitted due to exposure to a seafood market (Huanan Seafood Wholesale Market) 8. Up to now, there are no reports whether such exotic habits has been still practised during the epidemic of COVID-19. However, this review discussed several aspects of the possible persistent infection with SARS-CoV-2 that stand behind the reporting of new cases during the lockdown ever where confirming human-human transmission during the current epidemic. Post-epidemic, no prognosis can be withdrawn whether the zoonosis transmission could be a possible source. However, perhaps the world is full with surprising food habits, and no one could expect the breakthrough of viral epidemic with new viruses, unless the efforts have been biased toward investigating and exploring new viruses in meats of new exotic animals, particularly that the current history is the era of viruses dominance. Besides, it is not ensured that the people in some countries could stop contact or eat the meat of virus sources to cause outbreak the virus again6.

According to the history of zoonotic and avian pathogenic viruses transmission to human, the food habits of a specific population could be a threaten for the whole of humanity. In addition, looking for the sources of SARS-CoV-2 during the epidemic disclose a vast shortage in the efforts of researchers as well as local and global health authorities and organisations in prioritising their efforts to recognise and identify the possible pathogenic viruses that possibly transmitted from wild or household pets to human. Instead of taking actions during epidemics. The United Nations should take actions and promote authorities worldwide implant regulations to prohibit unusual food habits simultaneously with ongoing efforts to identify the possible biological threatens for humanity.

Nonstop transmission

Since new cases of SARS-CoV-2 have been reported during the lockdown, this proposes some missings in the dynamics of

transmission of the virus. Except for a principal human to human transmission method by droplet and contact, there is still limited knowledge about possible alternate transmission methods to guide clinical care 13. Attention for other possible routes should be paid, such as faecal-oral and urine oral route since there are positive results of RT-PCR tests of urine samples and anal swabs of infected patients 13,14. Therefore, improper sanitisation after toilet and inefficient disposal and hygienic measures during hospitalisation or home isolation might contribute to the transmission of the virus into healthy people. In the developed countries, however, suppose that hospitals follow strict sanitisation, sterilisation and disposal measures, this would be not efficiently and adequately followed by the developing countries due to low income to purchase sanitisers and masks or stay at home, poor disposal sanitary systems, low awareness and perception of people about COVID-19. Although the airborne hypothesis of virus transmission has not been yet supported, the rapid transmission of the virus necessitates not to be neglected at least in the environment of room of home, where mild and moderate cases are isolated.

The primary reproduction number (R0) of SARS-CoV-1 was < 1, while the R0 of SARS-CoV-2 is 2.2-2.6 with an epidemic doubling time of 6.4 implying that SARS-CoV-2 is more contagious 15. In a mathematical model, R0> 1 suggests a continued transmission of the virus, therefore, bringing the value of R0 below 1 need to reduce the current infection to half through preventing and controlling transmission for minimising the emerge of newly infected cases and save lives of people who are susceptible to develop severe cases of COVID-1915. According to a systemic epidemiological review, SARS-CoV-2 has R0 of either 2-3 or 1.9 to 6.5, incubation period of 4-6 days, and a serial interval of 4-8 days 16. Besides, the outbreak has been still in the early phases in several countries, and considerable uncertainty exists in regards to the ascertainment rate and asymptomatic rate 16. The estimates of R0 could indicate the fact of the presence of a vast number of asymptomatic and contagious infected people who needs to be detected. In contrast, the estimates of serial interval could be interpreted in terms of picking up the virus by a healthy person from an asymptomatic infected one, which would serially expand the transmission period for months. The emerging of new cases will continue since COVID-19 is characterised by morbidity, longer incubation period, asymptomatic and symptomatic contagious infected patients and susceptibility of re-infection.

Although authorities all over the world followed strict enforced preventive measures to contain the transmission of SARS-CoV-2, a challenge is arising whether the recovered patients may be at risk of being reinfected or at least the recovered patients probably remain actively contagious17-20. Accordingly, a hypothesis of a probability of either re-infection or persistent infection after recovery could be assumed according to the available data, albeit such data have been still controversial. What ever the probability of re-infection, this concern should be taken into consideration to be further investigated since

this might contribute to re-infection, which will lead to an increase in the burden of medical care cost. In the literature, the recovered (negatively confirmed RT-PCR test) discharged COVID-19 patients showed positive confirmed tests after hospital discharging within a time range of 2-22 days 21-28. To assess the hypothesis of re-infection, several issues should be discussed. Firstly, the positive confirmed test of the virus after recovery could be attributed to the incomplete clearance of viral RNA which result in moving the virus from the lower respiratory tract to throat or nose under the effect of cough reflex 23. Secondly, no enough neutralising antibodies in the recovered COVID-19 patients have been developed28 indicating that persistent infection after recovery is an indicator of lack immunisation against the virus, which needs longer time to develop 21. While the titer of neutralising antibodies mostly tended to be high from 10 to day 15 after the onset of the mild symptoms and remained throughout a two-week follow-up 20,28, the timing, magnitude and longevity of humoral immunity is not yet understood for SARS-CoV-2 20. However, the low titer of neutralising antibody suggests that recovery could be due to cellular immunity (T-cells) 28 arousing the significance of enhancing immunity, particularly that COVID-19 is associated with dysregulation of cellular immunity. Thirdly, the rate of misleading false-negative RT-PCR test at the time of discharge of recovered patients was reported to account for 41% which could be due to the dropping of the virus level to a low enough level to be negative or technical errors28,29. Hence, multiple confirmatory tests should be performed before the discharge of recovered patients 22. Accordingly, the hypothesis of re-infection of the same recovered patients sound like to be misleading, and it should be replaced by the hypothesis of persistent infection with a higher probability that recovered discharged patients are converted to be asymptomatic contagious carriers, which can contribute in transmit the virus to new healthy people. The former hypothesis necessitates authorities to pay attention for continuing post-recovery quarantine for at least one month with periodic hospital check-up by using RT-PCR test27a virus culture and serology 20,28. Since RT-PCR is unable to detect past infection, serological testing could add value if captured within the correct timeframe after disease onset due to its ability to detect both active and past infections beside its usefulness in rapid case identification 29,30. In brief, case detection of the persistent infectionin patients with mild symptoms should be imposed17.

Severity-contributed factors

While the focus on prevention of the transmission and cross infection of COVID-19, the possible infection that could coexist with COVID-19 (co-infection) has not been paid attention adequately 31, mainly that secondary infections were found in 50% of non-surviving COVID-19 31. Severe COVID-19 patients are vulnerable to opportunistic infectious pathogens constituting extra challenge in terms of enhancing survival rates31-37.

Reviewing the literature indicated that ICU-admitted COVID-19 patients caught several bacterial pathogens during ICU including Panton-Valentine leucocidin–secreting Staphylococcus aureus,Meningococcal pneumonia,group A Streptococcus, carbapenem-resistant Acinetobacter baumanni (CRAB), Haemophilusparainfluenzae, Moraxella catarrhalis, Legionella pneumophila, mycoplasma pneumoniae, Mycobacterium tuberculosis, Stenotrophomonas maltophilia38-48. Besides, other studies reported viral infection that coexisted with COVID-19 including influenza virus A, influenza virus B, Epstein-Barr Virus, picornavirus, metapneumovirus, Parainfluenza 4 virus 32,33,38,44,49-52. Most of the secondary infections were either opportunistic due to immune dysregulation during the time course of COVID-19, prior underlying chronic infection or nosocomial infection (contaminated ventilators and pipe of bronchoscopy) 35,45. Accordingly, co-infections of ICU-admitted COVID-19 patients with other common respiratory pathogens should be considered53, mainly that a little has been known about patterns of co-infection with other common respiratory pathogens in COVID-19. Moreover, rapid characterisation of co-infection is essential in the management and treatment of the severe COVID-19 cases, which could help save lives and improve antimicrobial stewardship throughout the pandemic 32,35 due to that the recognition of bacterial, viral or fungal infections with the existed COVID-19 cannot be distinguished from each other depending on the clinical and radiological diagnosis 31.

Before admission to ICU, checking up for possible underlying chronic bacterial infection, presence of latent or active tuberculosis and HIV should also be considered to avoid either exacerbation of the severity of COVID-19, delay the antibody response in plasma or delay the clearance of the virus 31,46-48,52,54,55. Therefore, it is recommended to perform sputum culture microbiological tests (considering safety measures during sampling), which could add value to a proper evaluation of co-infections31 before prescribing antibiotics, which render culture-based microbiological testing less sensitive 35.Furthermore,procalcitoninvalues were reported to be not substantially modified in patients with viral infections, which may add value in distinguishing patients with or without severe COVID1956. Since the procalcitonin values would remain within the reference range in several patients with non-complicated SARS-CoV-2 infection, any substantial increase would reflect a coexisted bacterial infection with COVID-1956. Nonetheless, the co-infection with endemic infectious disease in COVID-19 patients should be evaluated since endemic infections disease are different from a country to another 57.

From a systematic review of the current evidence of severity, three factors would contribute to the susceptibility of developing severe cases of COVID-19 including age, immunity characteristics and pre-existing health conditions 16.Although the entry of SARS-CoV-2 into immune cells has not been elucidated 15, there is evidence of activation of innate and adaptive immunity to defend

against SARS-CoV-2 resulting in cytokine storm as well as depletion and dysregulation of cellular immunity which lead to a serious challenge to save lives of COVID-19 ICU-admitted patients due to pulmonary failure and destruction as well as heart, liver and kidney injuries 58-61. In severe cases of COVID-19, there is a reduction in CD4+, CD8+ cells, NK (Natural killers), the frequencies of regulatory T cells (Tregs) (CD4+CD25+CD127lo), while the observed increase in B cells could be in part due to the depleted T cells 58,59,62. The former findings could be supported by histological evidence from dead patients who demonstrated lung interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, and multinucleated syncytial cells with atypical enlarged pneumocytes in the intra-alveolar spaces suggesting overactivation of CD8+ T cells 58.

In severe COVID-19 patients, several cytokines are overproduced including IL1B, IL-2RA, IL1RA, IL-6, IL7, IL8, IL9, IL-10,TNF-α, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEG 58,59,63. Conversely, a woman with a non-severe case of COVID-19 did not develop ARDS (acute respiratory distress syndrome) or respiratory failure, but showed an increased titer of IgG and IgM antibodies from day seven to day 20 of recovery, while TFH cells, CD4+ and CD8+ T cells increased from day 7 to day 9, then decreased by the day 20 64. The former findings could indicate that the severity of COVID-19 is exacerbated in part by depletion and dysregulation of the cellular immunity and the associated overproduction of cytokines.

COVID19 uses the same lung entry as SARS-CoC-1, which is ACE II (angiotensin-converting enzyme II receptors) in lung 6. Thus, the susceptibility to develop severe cases of COVID-19 could be related to the expression extent of ACE II in the lung, intestine and kidney, which could explain the reason behind the development of pulmonary, cardiovascular, renal, gastrointestinal complications in severe cases 13. Accordingly, smokers, patients with chronic pulmonary obstructive disease (COPD), diabetic patients and hypertensive patients are more susceptible to develop severe cases of COVID-19 due to the highly upregulated ACE II receptors 65-70.Another factor that might contribute to the severity of COVID-19 is the degree of virulence of the merged variants of the virus due to rapid mutation71. Coronaviruses have the largest genomic materials (genomes) (26.4 kb to 31.7 kb) among the whole other recognised RNA viruses supplying coronaviruses with extra plasticity in accommodating and modifying genes 72 due to the coding sequence of +ssRNA viruses biased toward GC content (directional mutation bias), which could theoretically predict the efficiency of viral gene expression in human cells 73. In addition, coronaviruses genomes show a broad genetic diversity and the ability to frequent recombine genomes which implies a significant public health challenge depending on the prediction of 24.5 genetic annual substitutions 74. Following the phylogenetic evolution of the SARS-CoV-2 virus during its journey from a country to another indicated the presence of three central variants of this virus within infected humans so that variant

A is the ancestral viral genomic version (the same as Bat coronavirus; BatCoVRaTG13), from which one lineage emerged called variant B due to one-step mutation drift, while another mutation drift of variant B resulted in emerging variant C 71. As SARS-CoV-2 infects humans, it is mutated with time to merge virulent variants of high mortality rates 9. Accordingly, a close monitor is recommended to detect whether the virus continues to evolve to become more virulent 6. Nonetheless, there are no data available about the correlation and association of the virulence of merged variants with the severity of COVID-19.

No effective preventive and curative interventions

One of the most genotypic features of the SARS-CoV-2 genome is the 80% similarity to that of SARS-CoV-1 (Severe Acute Respiratory Syndrome), 96% to the bat coronavirus (BatCoV RaTG132) and 50% to MERS-CoV (Middle-East Respiratory Syndrome) 9,74, which could recall the strategies for developing curative and preventive interventions against SARS-CoV-2taking into consideration the epidemiological factors and the specific genomic differences. Since the genetic material of SARS-CoV-2 and other coronaviruses show genetic drift, this reflects itself on the difficulties in developing effective selective specific preventive (Vaccines) and curative (therapeutic agents) interventions to stop the emergence of new cases and reduce the mortality rate among infected patients 74. Since the genetic material of coronavirus (SARS-CoV-1, SARS-CoV-2 and MERS-CoV) is a positive-sense mRNA single strand (+ssRNA) 9,73, the genome of SARS-CoV-2 is immediately translated by the host cell into new versions of the virus 73. The formal findings recall the approach of viral restriction that was developed by Mori, Nakamura 75 through RNA restriction enzyme using artificial SNase to cleave viral RNA staphylococcal nuclease, which could allow the SNase-fusion nuclease to cleave an RNA target in mammalian animal cells and/or organisms. Because the virus was not killed even if the patient received antiviral agents 24, there is no full effective and selective antiviral agent that can completely clear the virus up. Hence the virus will stay inside the body making asymptomatic or symptomatic mild, moderate or recovered COVID-19 patientsa likely contagious, which could in part support the persistent infection and the emergence of new cases.

Phylogenetic analysis of the genomes of SRAS-CoV-2 provides opportunities for understanding virus evolution within the human to help trace infection pathways and design preventive strategies 71. However, the subsequent mutation drifts enable the newly emerged versions of the original virus genome to escape recognition, hence the likeability to re-infection even after recovery. Another aspect of immunological events, the molecules of MHC I and II (major histocompatibility complex or HLA; human leukocyte antigen) on T cells initiate a human immune response to infections pathogens 11 through presenting the antigenic peptide of pathogens to CD4+ T cells 76. As the virus enters the cells, the antigenic peptide of the

virus is initially presented to APC (Antigen Presenting Cells) by MHC I and II to be recognised by virus-specific cytotoxic T lymphocytes 60. At this stage, the subsequent events in the antigenic presentation of SARS-CoV-2 have not been fully understood, and it could only be referred to the antigenic presentation of SARS-CoV-1 on MHC I. However, the role of MHC II in the antigenic presentation of SARS-CoV-2 has been still questionable 60. On the other hand, the genomic region that encodes MHC molecules in human is the most variable region, which could alter the genetic susceptibility to COVID-19 11, particularly that numerous HLA polymorphisms correlated to the susceptibility of SARS-CoV-1 60. Simultaneously to the activation of cellular immunity with MHC-antigenic presentation, the humoral immunity also being activated 60 by producing antibodies from B cells, particularly IgG and IgM 64.

In addition, understanding the molecular mechanisms of MHC-antigenic presenting function could be beneficial since supporting the immune defence is a goal of therapy 77.

The goal of immune therapy in terms of cytokine storm to stop further destruction of pulmonary, cardiac, liver and kidney injuries could be hypothesised to identify targets for immune therapeutics to reduce cytokine storm since the developed antiviral agents will not able to stop cytokine storm, relieve the inflamed alveolar mucosa and maintain the destroyed pulmonary architecture 62.

Conclusions

This is the era of viral foes against humanity, and no one could expect the breakout of the new viral epidemic unless the efforts have been oriented toward investigating and exploring new viruses in the wildlife and wet meats of exotic animals. Besides, it is not ensured that the people in some countries could stop eating unusual meat that could result in the outbreak of the virus again. Although the prolonged lockdown everywhere, the human to human transmission of the SARS-CoV-2 has been still active and new infected and dead cases have been still reported daily. Reviewing the literature provide several expected reasons that stand behind the daily reported new cases of COVID-19 due to transmission route other than oral droplets particularly faecal-oral and urine oral route of transmission of SRAS-CoV-2 since there is positive evidence of the excretion of the virus in urine and stool of infected patients. In addition, there is evidence of re-infection or persistent infection in the recovered patients due to incomplete clearance of the virus even after receiving antiviral treatment, infection by new mutated genomic variants of the virus or a lack of immunisation against the virus.On the other hand, the severity of COVID-19 resulting in the daily reported death cases could be due to connection with opportunistic pathogens (bacterial or viral), previously harboured pathogens, underlying chronic infections or nosocomial infections. Moreover, the severity of COVID-19 could be attributed to the emergence of highly virulent variants of the virus or highly

upregulated ACE II in hypertensives, smokers, underlying chronic chest infections or diabetics. Even after terminating the lockdown, people would not be able to restore their everyday life without maintaining personal sanitisation, social safe distance as well as wearing masks and gloves. Complete stopping and controlling transmission of the SARS-CoV-2 virus would be achieved through developing a safe and effective vaccine for immunisation and effective antiviral agent to clear the virus up from infected patients.

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