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Current community transmission and future perspectives on the COVID-19 process

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Background/aim: COVID-19 syndrome due to the SARS-CoV-2 virus is a currently challenging situation ongoing worldwide. Since the current pandemic of the SARS-CoV-2 virus is a great concern for everybody in the World, the frequently asked question is how and when the COVID-19 process will be concluded. The aim of this paper is to propose hypotheses in order to answer this essential question. As recently demonstrated, SARS-CoV-2 RNAs can be reverse-transcribed and integrated into the human genome. Our main hypothesis is that the ultimate aim of the SARS-CoV-2 virus is the incorporation to human genome and being an element of the intestinal virobiota.

Materials and methods: We propose that the SARS-CoV-2 genomic incorporation to be a part of human virobiota is essentially based on three pathobiological phases which are called as the 'induction', 'consolidation', and 'maintenance phases'. The phase of 'recurrence' complicates any of these three disease phases based on the viral load, exposure time, and more contagious strains and/or mutants. We have performed the 'random walk model' in order to predict the community transmission kinetics of the virus.

Results: Chimerism-mediated immunotherapy at the individual and community level with the help of vaccination seems to be the only option for ending the COVID-19 process. After the integration of SARS-CoV-2 virus into the human genome via the induction, consolidation, and maintenance phases as an element of intestinal virobiota, the chimerism would be concluded. The 'viral load', the 'genomic strain of the SARS-CoV-2', and 'host immune reaction against the SARS-CoV-2' are the hallmarks of this long journey.

Conclusion: Elucidation of the functional viral dynamics will be helpful for disease management at the individual- and community-based long-term management strategies.

Key words: SARS-CoV-2, COVID-19, virobiota, genomic integration

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of coronavirus family which leads to a respiratory disease like severe acute respiratory syndrome coronavirus (SARS-CoV). SARS-CoV and SARS-CoV-2 are from the same virus family origin and their features of structure, genetics, and pathobiology are similar to each other. Our research group had recently published that coronaviruses may affect pulmonary tissues and some critical immune genes play essential roles after their interaction with renin–angiotensin system (RAS) elements [1]. Local tissue-based RASs, for instance bone marrow (BM) RAS [2,3], serve for the dissemination of the SARS-CoV-2 infection for the genesis of COVID-19 syndrome associated with macrophage activation [4]. We have demonstrated that the RAS genes play a significant role at the initiation of the infections caused by coronaviruses and may have a strong association with the exchange of immune genes during the clinical course following the infection. On the other hand, there are ongoing discussions regarding the clinical course of COVID-19. Our team had proposed three critical prominent phases regarding the clinic-genomic course of the COVID-19 immune syndrome [5]. We have previously disclosed that the COVID-19 clinical course follows three consequent periods which are 'asymptomatic/presymptomatic phase',

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'respiratory phase with mild/moderate/severe symptoms', and 'multisystemic clinical syndrome with impaired/disproportionate and/or defective immunity'. ACE2 and ANPEP, EGFR and IGF2R, IFN and immune system-related critical gene involvements play a role in the first, second, and third phases, respectively. The separation of each phase from another with their own different genetic features enables researchers to focus more appropriately on the treatment of COVID-19. Comprehensive genomic profiling with next-generation sequencing may play an important role in distinguishing between the phases. Our group had also proposed potential treatment options for COVID-19. ANPEP gene pathway could be investigated for the vaccine development. MAS receptor agonists, TXA127, Angiotensin (1-7) and soluble ACE2 have the potential to interfere gene expressions thereby altering the COVID-19 disease course. The genomic editing by future CRISPR technology has also been discussed as a treatment option for COVID-19.

Since the current pandemic of SARS-CoV-2 virus is a great concern for everybody in the world, the frequently asked question is how and when the COVID-19 process will be concluded. The aim of this paper is to propose hypotheses in order to answer this essential question. Several papers had already pointed out modelling systems focusing on viral dynamics [6,7]. Zhang et al. recently demonstrated that SARS-CoV-2 RNAs can be reverse-transcribed and integrated into the human genome [8]. The authors even stressed that the current SARS-CoV-2 PCR tests are detecting viral transcripts from viral sequences stably integrated into the genome rather than active infectious virus. Thus, routine PCR tests may neither reflect actual active viral load nor the efficacy of the treatment to suppress viral replication [8].

2. Materials and methods

Our main hypothesis is that the ultimate aim of the the SARS-CoV-2 virus is the incorporation to human genome and being an element of intestinal virobiota. Prolonged SARS-CoV-2 RNA shedding and recurrence of PCR-positive tests are evident in asymptomatic healthy noninfectious individuals because of the viral sequences stably integrated into the genome [8]. Intestinal SARS-CoV-2 colonies are demonstrated during the long-term course as well [9,10]. We, herein, propose that the SARS-CoV-2 genomic incorporation to be a part of human virobiota is essentially based on three pathobiological phases which are called the induction, consolidation, and maintenance phases. This genomic incorporation is affected by three main factors which are the 'viral load', the 'genomic strain of the SARS-CoV-2', and 'immune reaction against the SARS-CoV-2'. The immune reaction against SARS-CoV-2 in the community actually represents the third phase of the clinical course of COVID-19 in human body which is previously described by our group as 'multisystemic clinical syndrome with impaired/disproportionate and/or defective immunity' [5]. In this phase, the immune system is impaired which means that it has lost its balance and malfunctioning so it leads to the either exaggerated immune response or immune deficiency. Herein, our group aimed to focus on the concept of 'human virobiota' and 'genomic incorporation' of the SARS-CoV-2 to human virobiota. All countries in the world are in the different genomic incorporation phases of the SARS-CoV-2 to human virobiota. The stage of genomic incorporation phase in the community is directly related with the mortality of the COVID-19 in each population. Integration of the viral genome into the host cell genome is a very complicated process [11]. Chimerism-mediated immunotolerance between the virus and human seems to be the only solution for this ongoing pandemic. Cellular immunity, particularly the T cells, could have the most significant impact on the generation of immune tolerance and host-virus chimerism [12–15]. The importance of protective mucosal T-cells against SARS-CoV-2 could take place within the chimerism-mediated immunity including the intestinal system [16].

The induction phase of genomic incorporation exerts all three phases of the COVID-19 syndrome in human body which are 'asymptomatic/pre-symptomatic phase', 'respiratory phase with mild/moderate/severe symptoms' and 'multisystemic clinical syndrome with impaired/disproportionate and/or defective immunity'. One exception of this is the COVID-19 syndrome in pediatric age. In children, COVID-19 generally presents with 'asymptomatic/pre-symptomatic phase', 'respiratory phase with mild/moderate/severe symptoms', and do not reach the last phase of the disease. The potential reason of this finding could be the unique gene expressions in each phase and the difference between the gene expressions of adult and child COVID-19 patients. The assumption is that the majority of the countries in the world will complete the induction genomic incorporation phase in summer 2020 and proceed to the consolidation phase of genomic incorporation of the SARS-CoV-2 to human virobiota.

The consolidation phase of genomic incorporation exerts generally the first two phases of the COVID-19 syndrome in human body, which are 'asymptomatic/presymptomatic phase', 'respiratory phase with mild/moderate/severe symptoms'. The phase of 'recurrence' complicates any of these three disease phases based on the viral load, exposure time, and more contagious strains and/or mutants. We assume that we are currently in the recurrence phase with the disease spreading in our community. We assume that the majority of the countries in the world will complete the consolidation genomic

incorporation phase in middle or late 2021, unless a phase of 'recurrence' does not complicate any given community because of the high viral load within a relatively short exposure time with more contagious SARS-CoV-2 strains and/or mutants [17].

We assume that the maintenance phase of genomic incorporation will exert generally only the first phase of the COVID-19 syndrome in human body which is 'asymptomatic/presymptomatic phase'. We have performed the 'random walk model' in order to predict the course of genomic incorporation stages of the SARS-CoV-2 to human virobiota.

COVID-19 death rate data is hard to forecast. We believe that these rates move like random walk. After taking first differences of the data, our data behaves like noise. Random walk model solves the uncertainty problem for more than 1 period. Our model also makes a benchmarking for the death rates. Random walk model is common in forecasting irregular time series data. Model forecasts the change between two periods. Therefore, the first difference of the series is a predictable pattern. Error terms must be independent and identically distributed (iid) in random walk model. The forecasted sample is independent from historical data. These models are denoted as below. Y_t is the value of forecasted data in time t, Y_{t-1} is the value that is one period before and error term is iid. is the autocorrelation coefficient that satisfies $|\rho| < 1$.

$$Y_t=\rho \times Y_{t-1}+\varepsilon_t$$

If we divide Y_{t-1} from both sides, then we have error term as the change between two periods which is independent from past movements (). Error term depends only on period t and t-1 values of Y. Then we have Y_t as denoted from Y_0. Here we do not have drift component.

$$\varepsilon_t=Y_t-Y_{t-1}$$
$$Y_t=Y_0+\sum_{i=0}^{t-1}\varepsilon_{t-i}$$

Our group estimates that after the middle of 2021, the pandemic will reach its last phase with an extensive spread throughout the world but a very low mortality rate compared to the first and second phases. In this last phase, SARS-CoV-2 will become a part of human virobiota and the human immune system will accept the presence of the SARS-CoV-2. Therefore, human immune system will not be reactive against SARS-CoV-2 that enables patients to have a much more improved clinical course. The patients will probably have a mild clinical course as the clinical course of an influenza virus (Figure 1).

During our analysis of the COVID-19 cases in large communities, we have found that besides the proposed three phases, there is another phase of 'recurrence' that emerged because of high viral load within a very short time period and/or different viral strains or mutants [18]. However, we suggest that this phase is temporary and communities will eventually return to the consolidation or maintenance phases (Figures 1–3). We also predict that maintenance phase of genomic incorporation to human virobiota will last around 5 years (Figure 3).

To show the alterations in IFN genes, GSE17400 data was normalized using the RMA method [1]. When the expression of genes belonging to cells infected with SARS-CoV for 12 h was compared with the group infected for

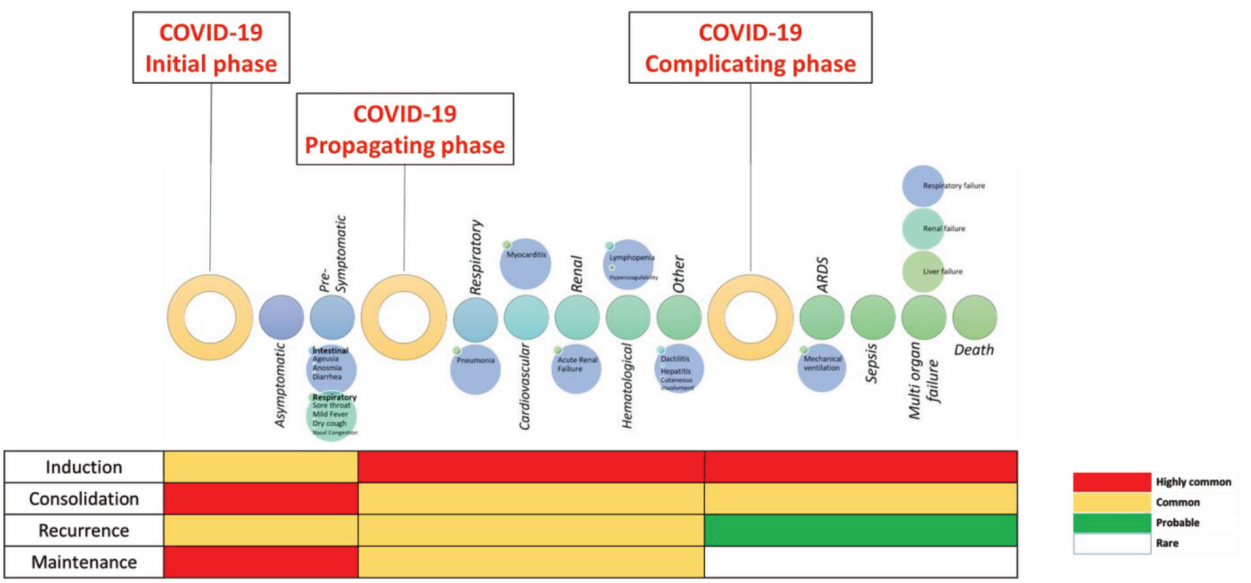

Figure 1. The proposed SARS-CoV-2 phases of genomic incorporation to human genome as a part of intestinal virobiota in large communities.

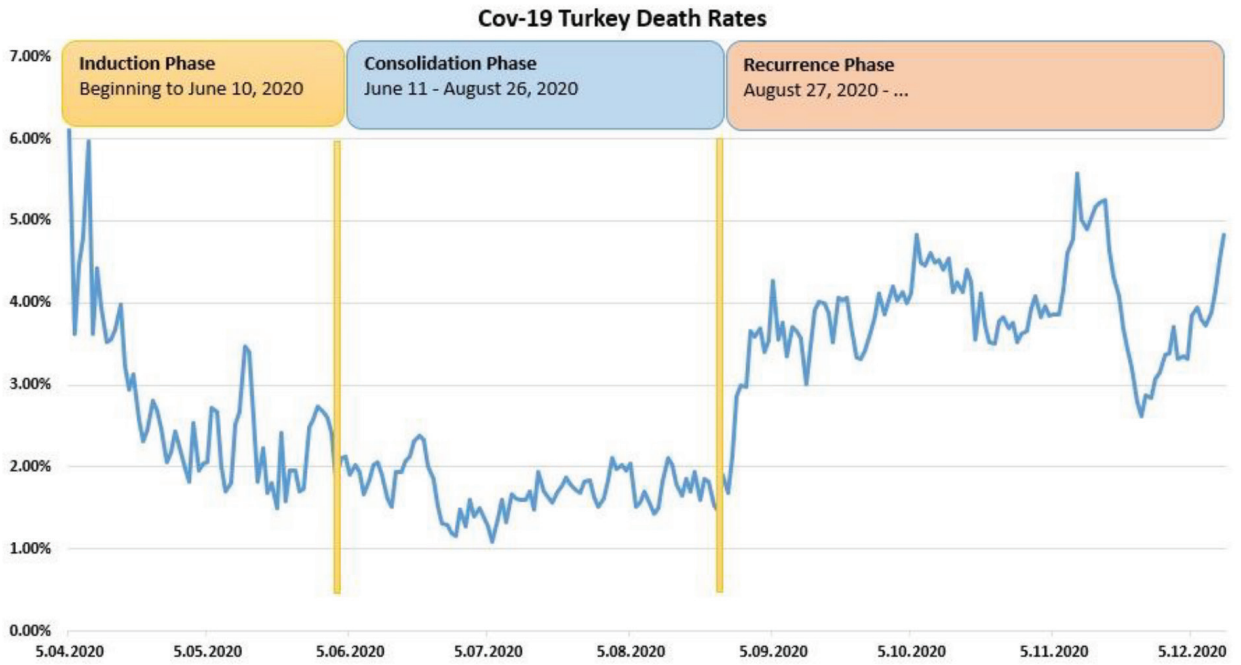

Figure 2. COVID-19 death rates in Turkey from beginning of the COVID-19 pandemic in Turkey. Induction phase of the COVID-19 has ended on 10th June 2020, and between 11th June and 26th August 2020 Turkey has experienced the consolidation phase of the COVID-19 pandemic. From 27th August, the recurrence phase of the COVID-19 has started in Turkish community.

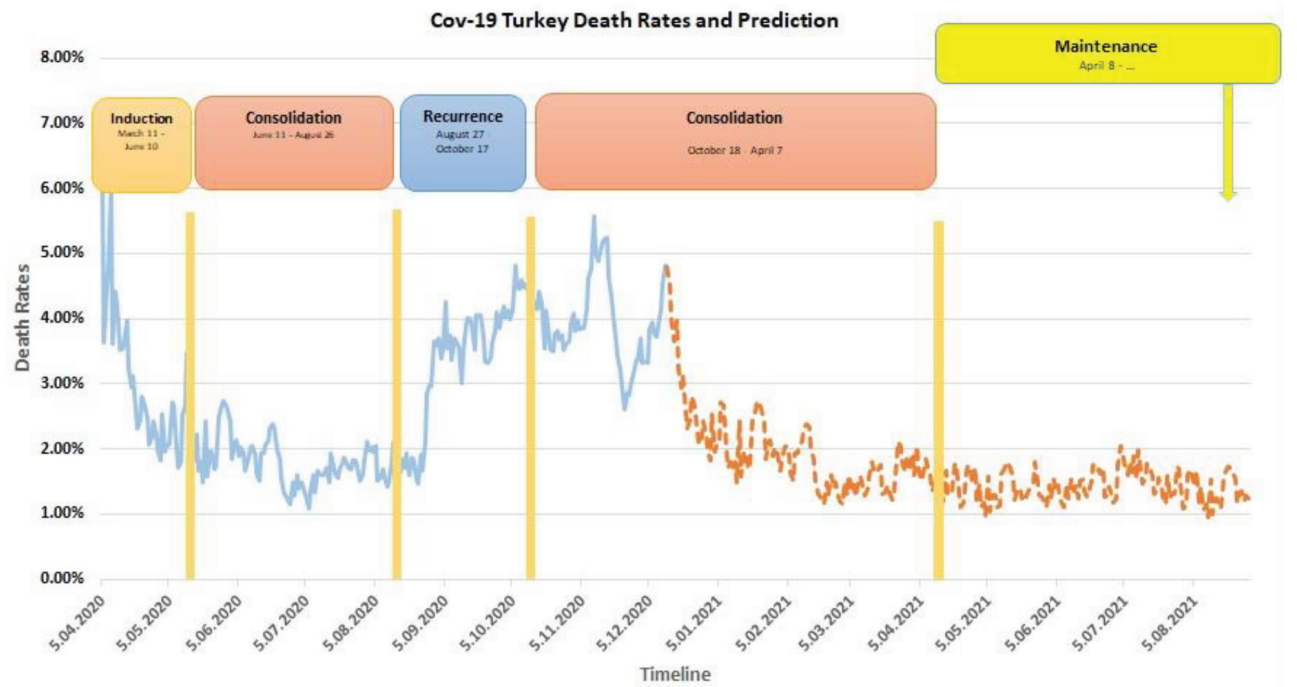

Figure 3. The prediction of the COVID-19 death rates in the Turkish community. We have applied the 'random walk model' in order to predict the course of genomic incorporation stages of SARS-CoV-2 in the Turkish community virobiota. We assume that the Recurrence phase ended in the middle of October 2020 and eventually Turkish community will return to the Consolidation phase. We have predicted that Turkish community would enter the maintenance phase in mid-2021.

48 h; it was determined that 34 probe sets belonging to 23 genes that were expressed statistically significantly and differently. Among these genes, a total of 17 genes were found to increase in expression as the virus treatment process progressed, while a decrease in the expression of other genes was observed (Figure 4).

3. Results

3.1. Evaluation of the 'three-phase' hypothesis

3.1.1. Initial phase of COVID-19

In this phase, the COVID-19 patients are either asymptomatic or presymptomatic. If patients are asymptomatic, they have no signs or symptoms and they

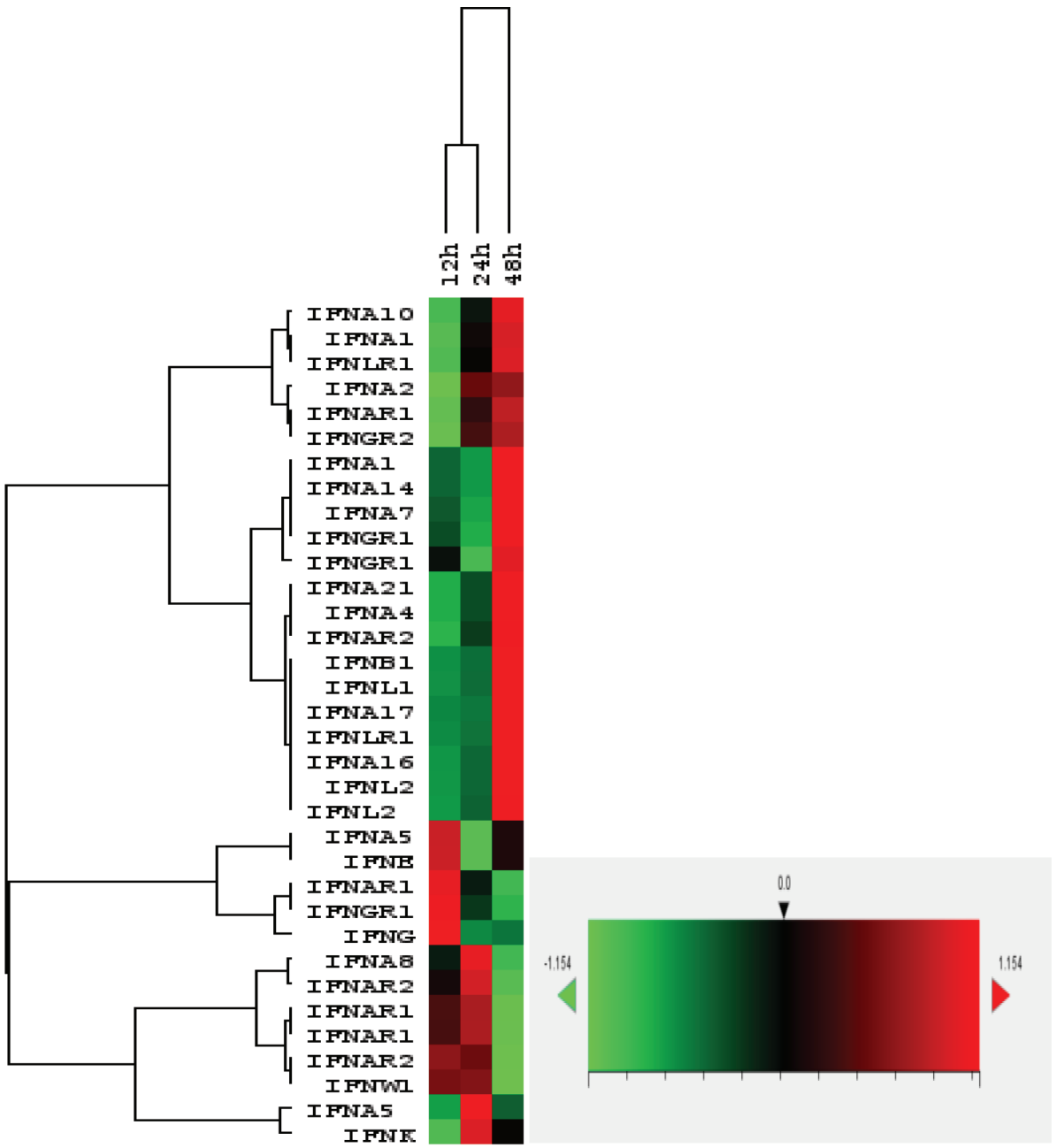

Figure 4. The expression of genes belonging to cells infected with SARS-CoV for 12 h was compared with the group infected for 48 h. It was found that 34 probe sets belonging to 23 genes were expressed statistically significantly and differently. Among these genes, a total of 17 genes were found to increase in expression as the virus treatment process progressed, while a decrease in the expression of other genes was observed.

complete the clinical course without any complication. If patients are presymptomatic, then they have either present with respiratory form or intestinal form. In the respiratory form of initial phase of the COVID-19, patients may have sore throat, mild fever, dry cough, and nasal congestion. In the intestinal form of initial phase of the COVID-19, patients may have ageusia, anosmia, and diarrhea. Our group previously published that ACE2 and ANPEP genes play major roles in the initial phase of the COVID-19 [5].

3.1.2. Propagating phase of COVID-19

In the propagating phase of the COVID-19, patients' symptoms start to worsen. They may have mild to moderate or severe symptoms. Many organ systems may be involved in this phase. Patients may have respiratory, cardiovascular, hematopoietic, renal and other organ system involvements. In the respiratory system, patients may have pneumonia and the involvement of lung tissue which can be confirmed by imaging techniques. In the cardiovascular system, patients may have arrhythmias, acute cardiac injury, and myocarditis [19]. In the hematopoietic system, patients may have lymphopenia and thromboembolic complications [20]. In the renal system, patients may have acute renal injury [21]. Moreover, in this phase, conjunctivitis, dactilitis, hepatitis, cutaneous involvements like maculopapular, urticarial, and vesicular eruptions, and transient livedo reticularis may be seen in the COVID-19 patients [22–24]. Our group previously published that EGFR and IGF2R genes play major roles in the propagating phase of COVID-19 [5].

3.1.3. Complicating phase of COVID-19

The complicating phase of the SARS-CoV-2 is the phase where the disease mostly ends up with mortality. In this phase, SARS-CoV-2 is already spread all over the body. Autopsy studies have noted detectable SARS-CoV-2 RNA (and, in some cases, antigen) in the kidneys, liver, heart, brain, and blood in addition to respiratory tract specimens, suggesting that the virus disseminates systemically [25]. In the complicating phase of SARS-CoV-2, patients are in severe and critical clinical condition. In this phase, the immune system is impaired, which means that it has lost its balance and is malfunctioning so it leads to the either exaggerated immune response or immune deficiency. Acute respiratory distress syndrome (ARDS) and multiorgan failure (MOF) are seen in most of the patients in this phase [19]. Patients are followed in the intensive care units and generally with mechanical ventilation support. Secondary infections are frequently seen in this phase which eventually leads to sepsis and septic shock [26]. Our group previously published that IFN and other immune genes play major roles in the complicating phase of the COVID-19 [5].

3.2. Empirical data

3.2.1. Human genomic incorporation of SARS-COV-2, a journey to the intestinal virobiota

In recent years, so as to comprehend the relationship between humans and viruses in more detail, the concept of virobiota become more popular. Virobiota generally implies a community of viruses. The physiological roles of virus population presences in the host are not fully known, while it is predicted that they attempt to survive in host cells. Some studies illuminate that human virobiota typically consists of some bacteriophages and mostly viruses. In addition to these, the mentioned partnership may have the potential to benefit the host depending on the functions of the viruses. On the other hand, it could also cause serious damage to the cells of the host [27–29]. One of the most significant biological steps affecting the host's virobiota is the incorporation of a virus's genome into the host. Proper understanding of the concept of genomic incorporation plays a crucial role in the development of this effect. This idea implies the transfer of the virus's genetic material to the target host; it also implies that this incorporation is critical for the survival of the virus's own functionality. For instance, once the virus transfers its genetic information to the host cell, it can propagate its numbers, which creates the possibility to replicate itself. In the genomic incorporation process, there are vital factors needing attention. Viral load, genomic strain, and immune reaction against the virus are three highly core factors [11,30].

Studies have shown that viral load has importance in the process of incorporating the genetic material of the virus to its target host. The data recorded in 2016 predicted that the viral load, which is not emphasized and cannot be determined in detail, may adversely affect the progress of the disease triggered by the virus. In another similar study, it was observed that high viral load in genomic incorporation increased the rate of disease development. This increased speed may cause the resistance of the cells to decrease and delay the immune response by putting pressure on the host cells. If infected individuals can alleviate the viral load triggered by the virus, they can also slow the progression of the disease. In that part, the immune reaction created against the virus infection could take place. These reactions can happen in two ways: immune depression and hyperinflammation due to overreaction between host and virus. These reactions have ability to lead to the serious process of genomic incorporation of virus [30,31].

In addition to the viral load and immune reactions, genomic strain of virus is another determinative factor for genomic incorporation of the virus, specifically SARS-CoV-2. According to a research, the strains of the SARS-CoV-2 virus are determined as an outcome of mutation. This will help to change the severity of the COVID-19

disease. The strains should be comprehended regarding the functionality of the genomic strains because this could change the entering criteria as well as genomic incorporation of the SARS-CoV-2 virus into host's cells. One mutation could make the SARS-CoV-2 virus more aggressive and then, some property of virus can alter regarding the transmissibility and severity [32].

A recent study depicted SARS-CoV-2 fecal viral activity in association with gut microbiota composition in patients with COVID-19 [16]. The result of this study favors that the middle- or long-term target of SARS-CoV-2 is to incorporate into the intestinal virobiota of the human body [16]. It is probable that intestinal local RAS system may play an important role in the genomic incorporation of SARS-CoV-2 to the human intestinal virobiata. In this study, we have applied the 'random walk model' in order to predict the course of genomic incorporation stages of the SARS-CoV-2 in the human virobiota (Figure 3). Intestinal SARS-CoV-2 colonization had recently been documented supporting our view of virobiota [9,10].

4. Discussion

4.1. Induction phase of the SARS-COV-2 genomic incorporation

As considering the stated information, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) incorporates its own genome to the human genome. This genomic incorporation performed by SARS-CoV-2 is predicted within the scope of this study that the induction phase plays a role in the part of genomic incorporation. The induction phase could be regarded as the first attack of the SARS-CoV-2 virus. The study conducted by Malkan et al. illuminated that SARS-CoV-2 acts in initiating, propagating, and complicating phases [5]. This virus was able to take place in initiating, propagating, and complicating phases during the time period of induction phase. The SARS-CoV-2 coronavirus primarily targets the ACE2 receptor. The reason behind this targeting is entering into cells as a result of causing alteration to the normal functions of ACE2. The ACE2 receptor enables S proteins to be activated and the stimulated S proteins support the SARS-CoV-2 virus to enter the host cells. With this entering, the virus could incorporate its genetic material into cells. Furthermore, during the entry time interval, the virus gains time for its replication. This incorporation can even be expressed as the initiating phase. Significantly, the change in expression is primarily observed in the lungs at the ACE2 protein level during this phase, which should be taken into account. Following the initiating phase, it is supposed that SARS-CoV-2 enters the propagating phase. This change also suggests progression to the lower respiratory tract. Additionally, the development could refer to changes in the expression levels of related different genes. In the same study, EGFR and IGF2R genes demonstrate the difference expression. The difference in the expression levels in both genes leads to the weakening of the activation in the innate immune system. The SARS-CoV-2 virus turns this weakening in its favor and accelerates the increase in numbers causing the severe damage to the host such as multiorgan failure. Alteration in gene expression levels that develop in the induction phase facilitates the entry of the SARS-CoV-2 virus into the host cell, leading to a weakening of the immune response that may occur early. Finally, it is known that there is a possibility that the SARS-CoV-2 virus may switch to the complicating phase during the induction phase. In this phase, the production of interferon as well as cytokine, which have a critical part in the development of immune response, changes cytokine production. Genes associated with immunity play an active role in the complicating phase, which can be regarded as the last stage of the induction phase. Differences in the expression levels of these genes can express the damage that the virus may cause. The cytokine and interferon produced constitute the first line of host defense despite the SARS-CoV-2 virus entering the cell [5,33].

In this induction phase, the lung is the main target for the SARS-CoV-2 virus. Generally, it causes pneumonia in this area. Pneumonia indicates specific inflammation that happens in the lungs. During this first attack, the human immune system dynamically works and the normal working function of T cell misleads take place in 3 phases [5]. The management of the induction phase of SARS-CoV-2 genomic incorporation could be achieved by test, trace, and isolate method. The suspected COVID-19 cases should be tested using appropriate methods and then the possible contacted cases should be traced, and finally the diagnosed cases should be isolated. This management strategy could be successful with the help of using masks, social distancing, and abiding by hygiene principles [34]. If needed, lockdown of the community may be used to control the disease in this phase of SARS-CoV-2 genomic incorporation.

The COVID-19 pandemic has been the subject of many scientific studies worldwide and in Turkey [35]. In the viral infection process, IFNs have important direct or indirect roles in the entry of the infectious agent into the host cell and its replication within the cell, and in the immune response that the host generates. In parallel with the results of studies conducted by other researchers, in our results, the symptoms and severity of the clinical picture in COVID-19 are directly related to the host's IFN response [5,36]. In the literature, it was proposed that early induction of IFN-γ-secreting SARS-CoV-2-specific T cells occurs in the COVID-19 cases with mild to moderate disease and accelerated viral clearance [37]. Intestinal SARS-CoV-2 colonization associated with IFN response as the critical step of the inclusion into the virobiota

usually follows the resolution of the clinical symptomatic viral infection.

In our results, while the expression of the 17 IFN genes is low at the beginning of the infection with SARS-CoV, as the time of treatment with the virus progresses, an increase in the expression of these genes is observed in lung epithelial cells. IFNAR2 from the type I interferon family and IFNLR1, a type III interferon, are two interferons that are effective in the viral replication process [36,38–41]. Two other important genes whose expression is increased as the exposure time to the infectious agent increases are IFNL1 and IFNL2 genes. High expression of these genes leads to an increase in the tumor necrosis factor [42,43].

Our results show that the expression of some genes in the interferon family is reduced as a result of infection progression. There may be different reasons for this. The generation of a measured IFN response can protect the host from the destruction of the proinflammatory response due to IFNs [44]. On the other hand, it has been shown that in some viral infections, the virus can inhibit the interferon release of the host [45].

4.2. Consolidation phase of the SARS-COV-2 genomic incorporation

Another genomic incorporation phase of the SARS-CoV-2 virus after the induction phase is the consolidation phase. The consolidation phase is assumed to occur in the upper respiratory tract, unlike the induction phase. The fact that the SARS-CoV-2 virus can pass to initiating and propagating phases constructs the basis of the consolidation phase. As stated in the induction phase, in the initiating phase, the SARS-CoV-2 virus tries to enter the host cells. The entering mechanism utilized by the SARS-CoV-2 virus is similar to the mechanism used by the SARS-CoV virus. The most significant of this similarity is the change in the expression level of the ACE2 receptor. Organs that increase ACE2 expression, such as the lung, are among the fundamental targets of the SARS-CoV-2 virus. The protein called spike or S glycoprotein associated with this receptor facilitates the virus to be incorporated. With the entry of the virus into the host cell, its genetic material is specifically transferred to the cytoplasm of the cell, and this transfer leads to an elevation in the number of replications of the virus. This rise in number aids to stimulate the immune response of the host cell [5,46].

When the virus progresses from the initiating phase, the functionality of the propagating phase emerges. This phase is perceived as the phase in which the damage produced by the virus is largely determined. During the propagating phase, a reduction in the expression levels of some immune-associated genes would be observed, as stated in the induction phase, and this decline correspondingly causes the immune response to be developed in the early phase. In the induction phase, the propagating phase was followed by the complicating phase due to severe damages that occurred at this stage. However, it is predicted that the complicating phase is not seen in the consolidation phase. In this case, changes occurring in the immune system at the molecular level take place as the main factor. With the activation of the S protein in the initiating phase, the mechanism of action of the Toll-like receptor 7 (TLR-7) located in the endosome during the genomic incorporation phase of the SARS-CoV-2 virus, becomes functional. Thanks to the active status of TLR-7, it supports the production of cytokines that is so crucial in the attack against the virus. In addition, with the aid of the activity of TLR-7, some signal pathways such as nuclear factor κB (NF-κB) and Janus kinase transducers (JAK / STAT) and transcription factors such as interferon response factor (IRF3), which are important under the influence of the virus, could be triggered. As considering these important pathways expressed as an example, the transition to the complicating phase can be prevented by presenting a noteworthy immune response due to the fact that the production of interferon and cytokine against the virus is strengthened at a certain rate. In fact, the decrease in mortality when examined from the first encounter time with the virus to the current period supports this situation [46].

The management of the consolidation phase of SARS-CoV-2 genomic incorporation could be achieved by test, trace, and isolate method. The suspected COVID-19 cases should be tested using appropriate methods and then the possible contacted cases should be traced and finally the diagnosed cases should be isolated. This management strategy could be successful with the help of using masks, social distancing, and abiding by hygiene principles. Lockdown of the community should not be used to control the disease in this phase of SARS-CoV-2 genomic incorporation.

4.3. Recurrence phase of the SARS-COV-2 genomic incorporation

In this temporary genomic incorporation phase of recurrence, communities exposed to high viral load within a very short time period and/or different viral strains. Appropriate management of communities will eventually lead to transforming the recurrence phase to the maintenance or consolidation phases. The management of the recurrence phase of SARS-CoV-2 genomic incorporation could be achieved using test, trace, and isolate method. The suspected COVID-19 patients should be tested using appropriate methods and then the possible contacted cases should be traced and finally the diagnosed cases should be isolated. This management strategy could be successful with the help of using masks, social distancing, and abiding by hygiene principles. Lockdown of the community should not be used to control the disease in this phase of SARS-CoV-2 genomic incorporation. Our country, Turkey, had been hit by that 'recurrence' phase

following the reopening of the community crowds, which was controlled via further restrictions and reinstitution of the wide test–trace–isolate strategy.

4.4. Maintenance phase of the SARS-COV-2 genomic incorporation

In addition to the induction and consolidation phases, maintenance phase could take place in the future period of SARS-CoV-2 infection. The clinical course of maintenance genomic incorporation phase in adult patients will be like the present COVID-19 clinical course in the children. In a recent study, it was reported that the SARS-CoV-2-specific IgA and limited inflammatory cytokines are present in the stool of selected patients with acute COVID-19 [47]. This study favors that the SARS-CoV-2 tends to incorporate into the intestinal virobiota. From our point of view, the maintenance period will probably start (probably in the spring of 2021) when the SARS-CoV-2 achieves the genomic incorporation into the homo sapiens' intestinal virobiota. In the literature, it was stated that 20% infected population is enough for achieving herd immunity [48]. Therefore, %20 SARS-CoV-2 infected population is necessary for community to achieve the maintenance phase of SARS-CoV-2 genomic incorporation. On the other hand, SARS-CoV-2 can have mutations which may facilitate the genomic incorporation of SARS-CoV-2 into human virobiota. In a recent study, it was found that a major deletion in the SARS-CoV-2 genome leads to a decrease in the severity of infection and the inflammatory response [49]. Another recent study also reports the evidence of mutations of SARS-CoV-2 [50]. These mutations may lead to acceleration in the transformation of communities into the maintenance phase of SARS-CoV-2 genomic incorporation. The maintenance phase of genomic incorporation could mimic the current pediatric SARS-CoV-2 clinicopathological course in adults with rare progression of the COVID-19 syndrome to terminal complication phase (Figure 1).

The most significant aspect of this phase is that the SARS-CoV-2 virus could display only the initiating phase, which was described in detail in the study of Malkan et al. [5]. Maintenance phase represents the entry of the SARS-CoV-2 virus into the host cell as well as the incorporation of its genetic material. After the genomic incorporation progression, it is predicted that the immune response described in the consolidation phase shows a significant increase in the functions of mechanisms with important functions such as TLR-7 and IFN3 at the molecular level. Moreover, it is believed that the damage caused by the virus in the host will be weakened thanks to this activation, and thus blocking the transition to severe phases such as propagating and complicating. In other words, this situation could allow the disease to be overcome presymptomatically. Besides, it is foreseen within the scope of this study that the SARS-CoV-2 virus can survive in the intestine, nervous system, and endothelial cells in the maintenance phase. According to some specific studies, the SARS-CoV-2 entering responsible receptor, ACE2 expressed in many different critical organs such as lung, intestine, heart as well as in endothelial cells. Furthermore, those studies and analyses underline the possible outcomes that the SARS-CoV-2 virus would be included under the human intestinal virobiota [47,51].

The management of the maintenance phase of SARS-CoV-2 genomic incorporation could be achieved by abiding by hygiene principles. Testing and tracing of suspected cases and isolation methods are not needed in this phase. Using masks and social distancing will not be necessary in this last phase of the disease genomic incorporation. If anytime an effective vaccine can be found for SARS-CoV-2, then the maintenance phase can begin earlier than mid-2021 or the reoccurrence phase can be prevented [52,53]. Maintenance phase could last 2 to 5 years based on the level of passive, active, natural community immunity. It is hoped that widespread vaccination against SARS-CoV-2 could be helpful for the shortening in the duration of the COVID-19 transmission phases.

5. Conclusion

COVID-19 syndrome due to SARS-CoV-2 virus is currently a challenging situation ongoing worldwide. Newly emerging mutant viruses such as United Kingdom variant B.1.1.7, South African variant B1351, and B.1.1.7+E484K mutant combination could produce their own induction–consolidation–maintenance–recurrence community phases with distinct virulence/mortality profiles. Overall infectious pattern and the resulting disease aggressiveness of the wild and mutant SARS-CoV-2 colonies will determine the global course of the pandemic within years.

Chimerism-mediated immunotherapy seems to be the only option for ending the COVID-19 process. After the SARS-CoV-2 virus is incorporated to the human genome via the induction, consolidation and maintenance phases as an element of intestinal virobiota, the chimerism will be concluded. The 'viral load', the 'genomic strain of SARS-CoV-2', and 'immune reaction against SARS-CoV-2' are the hallmarks of this long journey. Elucidation of the functional viral dynamics will be helpful for disease management at the individual- and community-based long-term strategies.

Conflict of interest

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