

Clinical complications and challenges during the follow-up of inpatients with COVID-19

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Abstract:

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), affecting people. Turkey was reported to the public by COVID-19 first cases of the Ministry of Health on March 10, 2020; and 520,167 cases and 14316 deaths were reported on December 03, 2020, respectively. The survival of these patients is usually determined over a 7-day intensive care follow-up. The survivors begin to recover clinically after the 15th day. So the riskiest period in terms of mortality is between 7-14 days. The antiviral called Favipiravir was administered only to intensive care patients in the first period and then allowed to patients in the clinic with oxygen saturation below 90% to achieve an improvement in the early period of patients with impaired oxygen saturation. But, it did not benefit patients with support with mechanical ventilation in ICU and their mortality rates. The cause of death is generally a respiratory failure due to the functional loss of lungs. Antiviral treatment is certainly needed to administer in the early period of disease to prevent a severe inflammatory response.

Key words: COVID-19; diagnosis; follow-up; complications

COVID-19 (COVID-19), long coronavirus disease 2019; an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), affecting people [1]. The disease, first discovered in Wuhan, China's Hubei province in 2019, has spread worldwide. Since its discovery caused a 2019-20 coronavirus pandemic. As of 9 May 2020, more than 3 759 967 cases have been reported across 187 countries and territories, resulting in more than 259 474 deaths. More than 1.31 million people have recovered. [1, 2] Turkey was reported to the public by COVID-19. The Ministry of Health reported the first case with covid-19 on March 10, 2020, and 520,167 cases and 14316 deaths were reported on December 03, 2020 respectively. [3]

Super silent spreaders are active in the viral transmission. Because, super silent spreaders, whose immune response is insufficient or unreturned, allow the virus to reproduce silently and that is a major factor in the spread of the disease. [4, 5] According to our observation, the virus binds to the upper respiratory epithelium and reproduces itself. [6, 7] After that it makes its first viremia, infecting almost all organs such as lung, brain, intestine, muscles, vascular structure, after viremia, and revealing related clinical pictures. [8-11] In other words, we do not think that the virus reaches the lung and creates an infection. If this were the case, there would not be so many patients, due to the spread of the virus and the number of infected people. Since the amount of virus that would reach the lung was prevented by physiological barriers.

Clinical and radiological findings were more helpful in diagnosing patients, since the result of the PCR test was concluded 1-2 days after application. Although the PCR test was negative, we found that patients with clinical and thoracic tomography findings were predominant. CT is more sensitive in diagnosis than the PCR test (Another issue is the situation of people who have no clinical findings, but who have PCR positivity. First, the false positivity of the PCR test, unfortunately, did not allow questioning due to the severity of the pandemic during this period. It will be useful to evaluate samples, such as oropharynx, nasopharynx, sputum, etc. and to support the results with antigen screening tests to reveal false positivity of these individuals. [12, 13] We suppose that these people have the real PCR positivity, so is this action in the transmission? As we have the case of Tuberculosis disease, sputum PCR samples remain positive for some time in patients receiving tuberculosis treatment, although sputum culture and smear tests are negative. We know that the PCR positivity here is not infectious. In this case, can the PCR Covid-19 viral load value be taken into account? Because, how effective is it in transmitting low PCR positivity? Is it infectious?

The Republic of Turkey, Ministry of Health has published a COVID-19 treatment guideline to avoid treatment chaos in the management of patients with COVID-19. [14] According to the guideline, hydroxychloroquine + azithromycin + oseltamivir (due to the Influenza season) was initiated to patients with clinical and/or radiological findings

and hospitalized in the first months of pandemic until the PCR test results were obtained. [14] Hydroxychloroquine did not prevent the development of infection, as COVID-19 developed in patients who receive that drug for the treatment of Systemic lupus erythematosus. Moreover, that drug did not reduce the intubation need of patients whose oxygen saturation was impaired or subsequently deteriorated. These patients were over the age of 50 and had at least one chronic disease. [15, 16] Only one patient who was receiving azithromycin and hydroxychloroquine therapies developed a QT-prolonged arrhythmia. And another patient developed acute renal failure. Other patients tolerated these two drugs comfortably.

Favipiravir, which was later brought from China by the Ministry of Health and was administered only to intensive care patients in the first period, and then patients with oxygen saturation below 90% in the clinics to benefit in the early period. But it did not benefit patients followed up in ICU and reduce the mortality rates in patients supported with mechanical ventilation. [17] It is suggested that the impaired immune system and physiological barriers of patients due to chronic diseases and risk factors could not provide an adequate response against the virus facilitating the development of sepsis and causing the body defeated in the struggle against COVID-19 when the burden on the body caused by sepsis is added to the weak body. [18] Favipiravir is administered for a total of five days, but the clinical deterioration period develops in the next period. In spite of favipiravir the clinical deterioration does not end, as the inflammatory response or attack continues. It turns out that even if the proliferation of the virus is prevented by favipiravir. The virus related structures trigger the inflammatory response strongly and constantly.

There is a need for an antiviral treatment that could be administered in the early period and prevent a severe inflammatory response. Secondly, the virus causes different clinical presentations in patients with COVID-19. The severity of the disease may be related to not only viral load but also subtypes of the virus, as with Influenza viruses. Therefore, those subtypes cause a different virulence and immune response. The subdivision of the global SARS-CoV-2 population was defined well in sixteen subtypes by focusing on the widely shared polymorphisms in nonstructural cistrons (nsp3, nsp4, nsp6, nsp12, nsp13, and nsp14), structural (spike and nucleocapsid) and accessory (ORF8) genes. Six virus subtypes were reported to be predominant in the population, but all sixteen showed amino acid replacements which could have phenotypic implications. [19]

A significant portion of inpatients was male with rates of 60% at our hospital. The course of infection caused by COVID-19 was not serious in patients who were between 18 and 50 years old and had no underlying disease. The prominent features of the patients followed up in ICU is the age over 50 years old (80% of them), being male and possession of at least one underlying disease (such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, heart failure, chronic kidney failure, obesity, Alzheimer's disease, etc.). The survival of these patients is usually determined over a 7-day intensive care follow-up, and the survivors begin to recover clinically after the 15th day. So the riskiest period in terms of mortality is between 7-14 days. The cause of death is generally a respiratory failure due to lung function loss. In the intensive care unit (ICU), almost all patients are older than 50 years old and have one or more risk factors. Therefore, almost all of the patients who do not have risk factors under the age of 50 recovers, even if the clinical presentation is severe. [20]

There was no relationship between increased D-Dimer values and a need for mechanical ventilation, high values of D-Dimer up to 80000 $\mu\text{g/L}$ returned to normal during the follow-up. Before anticoagulant use was recommended by the Ministry of Health treatment guideline, patients with very high D-Dimer values did not develop a pulmonary embolism during the hospital follow-up period. Two patients, who were younger than 50 years old, were admitted to the hospital with pulmonary embolism

and COVID-19 infection. In one patient, a pulmonary embolism developed 5 days after discharge. Anticoagulant therapy was routinely performed on inpatients who were over 50 years of age and those with underlying disease, and pulmonary embolism was not detected. The diagnosis of pulmonary embolism was performed as a result of CT-Angiography and these patients were discharged with anticoagulant treatment without any complications. It was observed that increased D-Dimer value is a component of vasculitis caused by COVID-19. Those values returned to normal range with the recovery of the disease during the period when anticoagulant use was not routinely. However, it will be beneficial to start anticoagulants in terms of complications that may develop if this vasculitis is more than 50 years old, with underlying disease, and with D-Dimer value above 2000 $\mu\text{g/L}$. [21]

Neurological symptoms (such as agitation, personality changes, lower limb paresthesia, ataxic movements) are also observed due to the formation of meningoencephalitis and meningomyelitis together with the vasculitis table of this virus. [22, 23] The reporting of Guillain-Barre syndrome cases related to Covid-19 supports this. [24] The long duration of these neurological findings supports the fact that the PCR result of patients is negative during the periods when the PCR result is negative. Symptomatic treatment for neurological findings shows benefits in patients.

CRP values are generally above 50 mg/dl at first admission in patients with Covid-19 regardless of bacterial infections. Therefore, it would be appropriate to consider leukocytosis and elevated procalcitonin value more in terms of bacterial infection. If there is a history of COPD and asthma in patients with extensive lobar or lobular infiltration on thorax CT, care should be taken in terms of secondary bacterial pneumonia, and antibiotics should be initiated. Although azithromycin is in the Covid-19 treatment guideline of our country, a beta-lactam antibiotic (ceftriaxone or cefotaxime) should be started by evaluating the clinical findings in patients with leukocytosis due to macrolide resistance in pneumococci.

It has been observed that third-generation cephalosporins are sufficient for the treatment of bacterial pneumonia, which develops secondary to the development of complications due to extending the length of hospitalization in intubated patients. However, in patients with increased leukocytosis and higher procalcitonin values, tazobactam-piperacillin and carbapenem may be included in the selection of broader spectrum antibiotics for the treatment of complications during the prolonged intubation time. Also, in intensive care patients, fever is seen as a part of Covid-19 infection, and it is not necessary to start a broad-spectrum antibiotic. Fever rarely extended to 10-14 days after the 7th day and then spontaneously decreased. For this reason, in patients followed up with Covid-19 in intensive care, a fever could be encountered as a part of viral disease rather than a bacterial infection. Blood cultures of patients with fever yielded no bacteria in patients with fever, until the length of stay at the intensive care unit as being intubated prolonged and secondary infection as a complication of prolonged intubation.

Although there are high expectations regarding vaccination, the following two issues will probably come up: First, whether the immunization rate in Coronavirus vaccine will be at the expected level or not, even the efficacy rates of the Influenza vaccine did not exceed 40-60%. [25] It is also a known fact that antibody response to inanimate vaccines is weak in older people. Therefore, if a certain level of at least 60-70% of the population is obtained with a vaccine to be produced, at least the spread of the virus will decrease, but the risk will continue for those with advanced age and underlying disease. Therefore, the availability of a drug is more important in this age group because the disease is more mortal. Again, mutations are reported in Covid-19 with such high replication and spread rates. Therefore, it is known that the vaccine will not have any effect after some time with the accumulation of these mutations.

Finally, everybody asks "When will this pandemic end? ". I think this question could be answered in two sentences: First, let's not forget that the first SARS outbreak that occurred in 2003 ended in 2005, about a year and a half. Secondly, even though it is reported that the number of cases in a country has decreased or not, it should be noted that in a world where borders are almost removed by travel, this epidemic may have ended all over the world.

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This article includes my personal observations that I have performed during my duty in Taksim Training and Research Hospital with 200 clinic beds and 38 intensive care beds, were covid-19 patients were followed, and published studies.

Conflict of Interest

There is no conflict of interest.

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