

ORIGINAL ARTICLE

Effect of COVID-19 on liver transplantation in Korea

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Abstract

COVID-19 is now a pandemic with increasing numbers of cases and deaths. In addition to the economic and social damage caused by COVID-19 outbreak prolongation, damage caused by delayed treatment of other diseases such as severe cirrhosis is also serious. We aimed to describe the effect of COVID-19 on the number of liver transplants (LT) in South Korea. The number of LT performed in Korea during the Middle East Respiratory Syndrome (MERS) outbreak, and the COVID-19 pandemic was compared with the average number of LT performed in the past 5 years. There were 108.5 cases of LT performed per month during the MERS outbreak. It was 11% lower than the average of 122.8 cases per month for the last 5 years. LDLT and DDLT decreased by 13% to 75.3 cases and by 7.5% to 33.2 cases per month during the MERS epidemic, respectively. From January to March 2020 (COVID-19 outbreak), the number of LT did not decrease significantly. The lockdown caused by COVID-19 did not affect the number of liver transplants in Korea. Establishing a safe process and procedure of liver transplantation within safe boundaries can be beneficial in reducing the side effects of lockdown and saving patients' lives.

1 | INTRODUCTION

MERS (Middle East Respiratory Syndrome) outbreak is a unique case of infection occurred in Korea 2015. The first infected person was a 68-year-old man who returned from a business trip in the Middle East, and by November, there had been a total of 186 patients and 38 deaths. Two infected people died in the first 12 days after the outbreak. The mortality rate is much high (14%), because most of infection occurred in local closed hospital. At the time, due to the lack of initial response, the number of infected patients increased rapidly, and in some cases, the medical institution in which the infected person occurred was undergoing the shut down. In addition, the government's passive reaction and censored information disclosure have caused social anxiety. After about 7 months and the government declared the end of MERS, the Korean government and the people who had suffered the MERS outbreak recognized the importance of the national isolation

quarantine wards and felt the importance of early prevention system for preparing viral pandemic.

In this COVID-19 outbreak, Korean government responded faster than any other country in the world and established a quarantine system and showed a decrease in the number of confirmed patients in a short time because of the lessons learned from previous MERS outbreak.

The campaigns of "lockdown" to restrict community activity, such as restricting all kinds of movement and social activity, and recommendations to wash hands, and wear masks have been employed worldwide.⁵⁻⁷ As a result, economic indicators have declined and the economic losses of the self-employed businesses, domestic industries, and global trading companies have been increasing.^{8,9} Meanwhile, in the United States, it has been announced that the schools will be closed for a semester. In Korea, the school opening has been delayed, and also recent pediatric cases of COVID-19 have been confirmed; thus, it is unclear whether schools will be opened

Abbreviations: COVID-19, coronavirus disease-19; DDLT, deceased donor liver transplantation; KCDC, Korean Centers for Disease Control & Prevention; KONOS, Korean Network Organ Sharing; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-stage Liver Disease; MERS, Middle East Respiratory Syndrome; MERS, Middle East Respiratory Syndrome; WHO, World Health Organization.

soon. Besides, no results from a remarkable treatment have been reported, and clinical trials are still in progress, so this situation is inevitable and prolonged until promising results are released.

In Korea, with the fast response and active movement of Korean Centers for Disease Control & Prevention (KCDC) and a quick scan using the test kits, the number of daily confirmed cases is showing a linear increase rate instead of an exponential rising in the cases graph, and the confirmed cases incidence rate is also now decreasing. Despite the declining number of domestic transmissions, the proportion of people returning from foreign countries has increased; thus, it is time to set a new strategy for a worldwide prolonged COVID-19 pandemic.

Medical resources are currently concentrated on COVID-19, and medical resources are redistributed according to the situation in each country. In Korea, infection control systems have been established around Daegu, where a group of infected people has been detected, and treatment is performed using a nationally managed quarantine bed according to the severity of the disease.

Besides the economic and social damage caused by the prolongation of the COVID-19 pandemic, the damage caused by delayed treatment of other diseases like malignancy and life-threatening severe cirrhosis is also serious. The mortality risk of a patient waiting for an LT increases daily until they receive an LT. Especially, in the case of DDLT candidates, organs are distributed through the Model for End-stage Liver Disease (MELD) score.¹⁰⁻¹³ The longer the waiting period until transplantation, the worse the condition becomes, and the MELD score increases, which results in poor outcomes after transplant.¹⁴ If the outbreak of viral diseases such as COVID-19 reduces the mobility of medical staff and the searching process for potential donor candidates, the probability of receiving a liver for transplantation is inevitably reduced. There is no doubt that the reduction of social activities and the imposed meeting restrictions due to COVID-19 have a great effect on suppressing the spread of this viral disease. The complete blockade will sometimes be the best solution, but as the pandemic period is prolonged we have to think about the opportunity cost. As transplant surgeons, we have to think about how we can perform a liver transplant (LT) as safely as possible during the pandemic period.

After organ transplantation guidelines from the Korean Network for Organ Sharing (KONOS) and the Korean Society of Transplantation have been established and shared, liver transplantation is currently officially in progress at most transplant hospitals, except for hospitals where the COVID-19 has occurred at a large scale.

The purpose of this study was to investigate the changes in liver transplant activity during the MERS and COVID-19 periods, two unique outbreaks that greatly affected the Korean government and people and to discuss about how it had been treated and handled to date, and how long it would last. And also I would like to discuss appropriate measures to cope with the prolonged period of this pandemic.

2 | METHODS

Using the KONOS database, we investigated the number of living and deceased donor liver transplantations performed in Korea between January 2015 and March 2020. I reviewed organ transplant guidelines and related literature recommended by the Society for Transplantation. And for statistical analysis, I reviewed the number of people infected with COVID-19 dated by the Korean Center for Disease Control and Prevention (KCDC). The changes in the number of liver transplants during the Middle East Respiratory Syndrome (MERS) outbreak from May to October 2015 in Korea, and the COVID-19 pandemic from January to March 2020 was compared with the average number of LT performed in the past 5 years and 1 month before each outbreaks. The reason for focusing in the first month when each outbreaks occurred (May when MERS occurred. January when COVID occurred) is that the initial response is the strongest, and this policy movement, and the anxiety of patients are most reflected in the initial outbreak and clustered infection.

For statistical analysis, SPSS ver. 22 (SPSS Inc) was used and analysis through variance comparisons was made for each group. In case the *P*-value <.05, it was considered to be statistically significant.

3 | RESULTS

3.1 | Trends in the number of LT per month in the last 5 years

Between January 2015 and March 2020, the total number of liver transplants (LT) was 7808 and the average monthly number was 122.8 ± 13.6 . Regarding living donor liver transplantation (LDLT), the total number was 5534 cases and the mean monthly number was 87.9 ± 12.9 cases. There were 2274 deceased donor liver transplantations (DDLT) and an average of 36.1 ± 7.2 cases per month. Also, the average annual growth rate of LDLT was 5.9% and the annual number of DDLT decreased to -3.0%, showing that the total number of liver transplants increased by 2.9% over the 5 past years (Figure 1).

3.2 | Difference in the number of monthly transplants between the MERS epidemic period and the COVID-19 pandemic period

When comparing the average monthly number of liver transplants from 2015 to 2020, there were 108.5 cases of LT a month in the period of MERS outbreak, which was 11% lower than the average of 122.8 cases per month for the last 5 years. During the MERS epidemic period, the number of LDLT and DDLT cases decreased by 13% to 75.3 cases on average, and by 7.5% to 33.2 cases per month, respectively. The number of both DDLT and LDLT fell sharply during the first month of May 2015, when the outbreak of MERS occurred. However, from June to October, when the MERS outbreak was

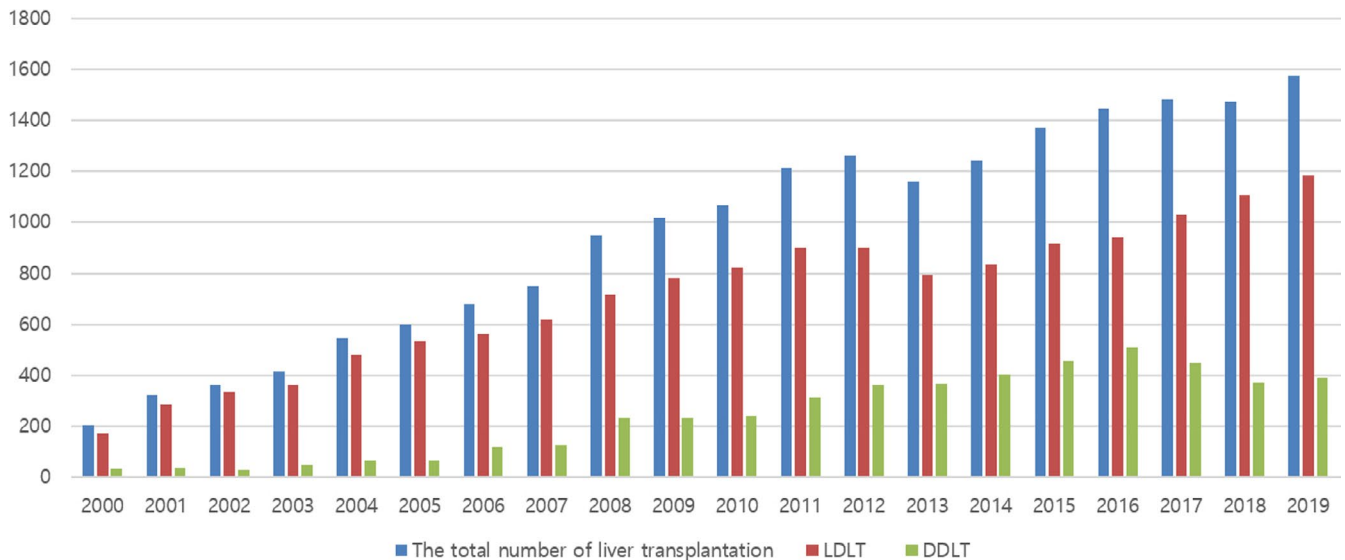


FIGURE 1 Annual number of LT in Korea

finally finished, the number of LT had recovered to a similar number observed in the previous year. The average MERS rate decreased by 11.1% from the previous 5 years and decreased by also 11% from the previous year, 2014.

On the other hand, from January to March 2020, the period of COVID-19 outbreak, the number of LDLT and DDLT cases did not decrease as expected even in the first month of the outbreak. The average number of LT increased slightly to 135.0 cases per month but did not show a statistically significant difference. During the COVID-19 pandemic period, LDLT increased by 16% to an average of 101.7 cases, and DDLT decreased by 5.9% to 33.3 cases, but it was not a statistically significant difference. None of the 401 patients who underwent liver transplantation during the outbreak period of COVID-19 were confirmed with COVID-19. There was only one donor who was positive for COVID-19 after donation but the recipient of that liver had no COVID-19 infection and the donor recovered well and was discharged without any complications related to COVID-19 infection (Figure 2).

At the time of the COVID, the average increased by 9.6% compared with the average in the 5 years, but decreased by 3% compared with the previous year, but it was not a statistically significant decrease.

3.3 | Number of transplantation and COVID-19 confirmed patients along the timeline

This is the daily graph of the number of confirmed COVID-19 cases and the number of living donor and deceased donor liver transplantations since the first COVID-19 case was confirmed in Korea (Figure 3). The first COVID-19 patient occurred in Korea on February 20. After clustered infection started from 31st patient at February 20, the number was reaching a peak of 909 people on the February 29th. World Health Organization (WHO) pandemic declaration was

announced on March 11th, and the Korean Society of Transplantation announced the recommendations regarding COVID-19 prevention during transplantation 1 day after the declaration of the COVID-19 pandemic from WHO. In the recommendations, it was specified that the recipients and donors of liver transplantation had to be tested for COVID-19 and that if the results were negative, liver transplantation could be performed. Since February 20, when there was a large-scale increase in the confirmed cases, the recommendations of social isolation at the national level have expanded and the guidelines of the transplant society have been shifted from the recommendation to the mandatory level. Even when the number of confirmed COVID-19 cases suddenly occurred, the numbers of deceased and living donor liver transplants remained the same.

3.4 | Difference in number of LT by region between the MERS and COVID outbreaks

There are 55 transplant centers in Korea where liver transplantation can be performed (Figure 4). In the city where COVID-19 infection incidence was massive, major medical centers entered an emergency state during the initial outbreak in which medical resources were invested into COVID-19; thus, it was difficult to proceed with liver transplantation. However, most of the transplants are usually performed at the major 5 Hospitals located in Seoul (64%); thus, the number of total cases was not reduced. During the MERS outbreak period, the number of total cases in the initial stage was slightly decreased because the hospital ranked 3rd in the total number of liver transplants performed in Korea was affected by MERS patients; therefore, normal medical service was blocked due to MERS outbreak.

Organ distribution in Korea is divided into three areas. The total number of cases was initially reduced in the third most affected region by COVID-19 compared with the same period of the previous year,

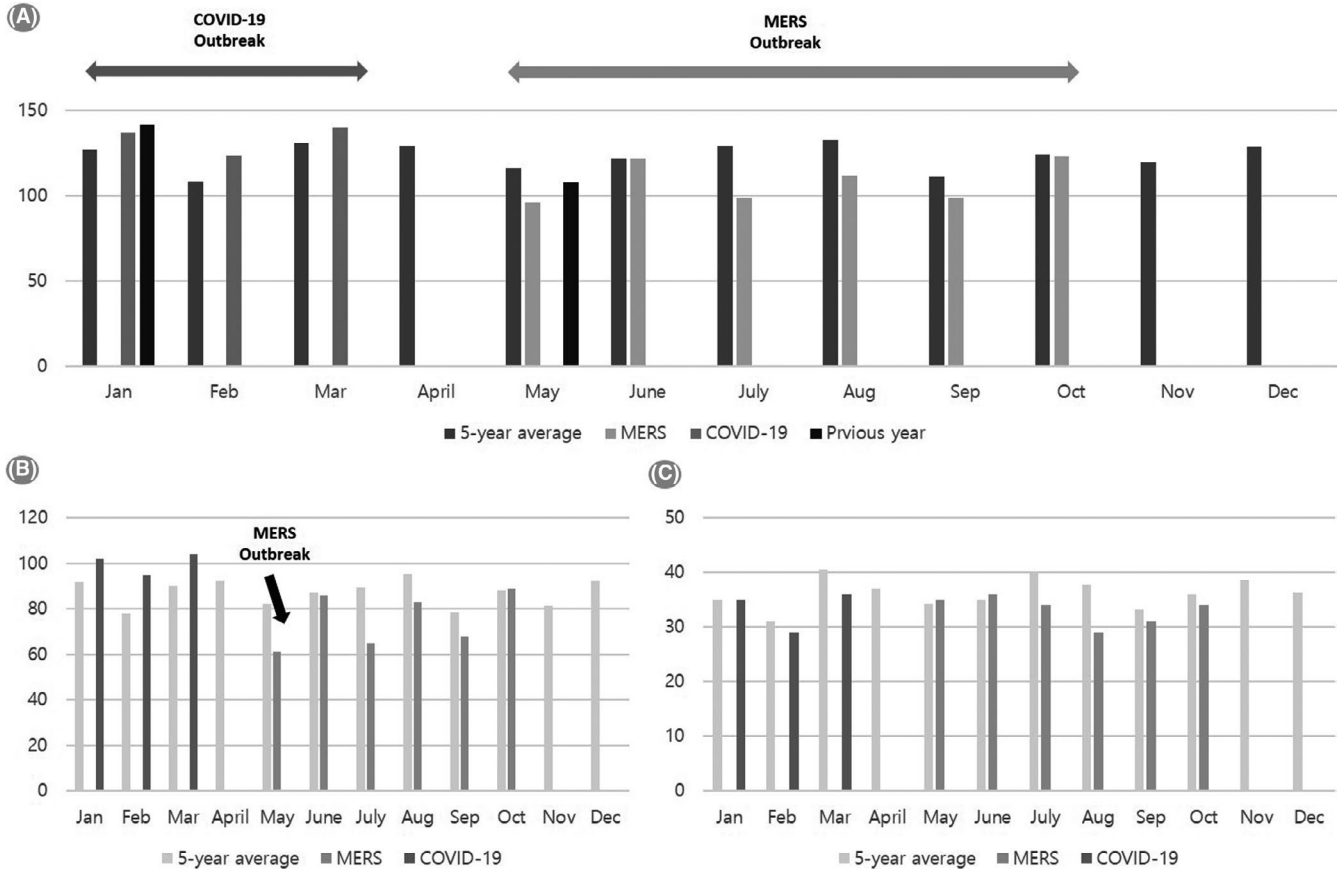


FIGURE 2 The difference in the number of monthly transplants between the MERS epidemic period and the COVID-19 pandemic period. A, Total number of LT in Korea between the MERS epidemic period and the COVID-19 pandemic period. B, The difference in the number of monthly LDLT cases. C, Differences in the number of monthly DDLT case

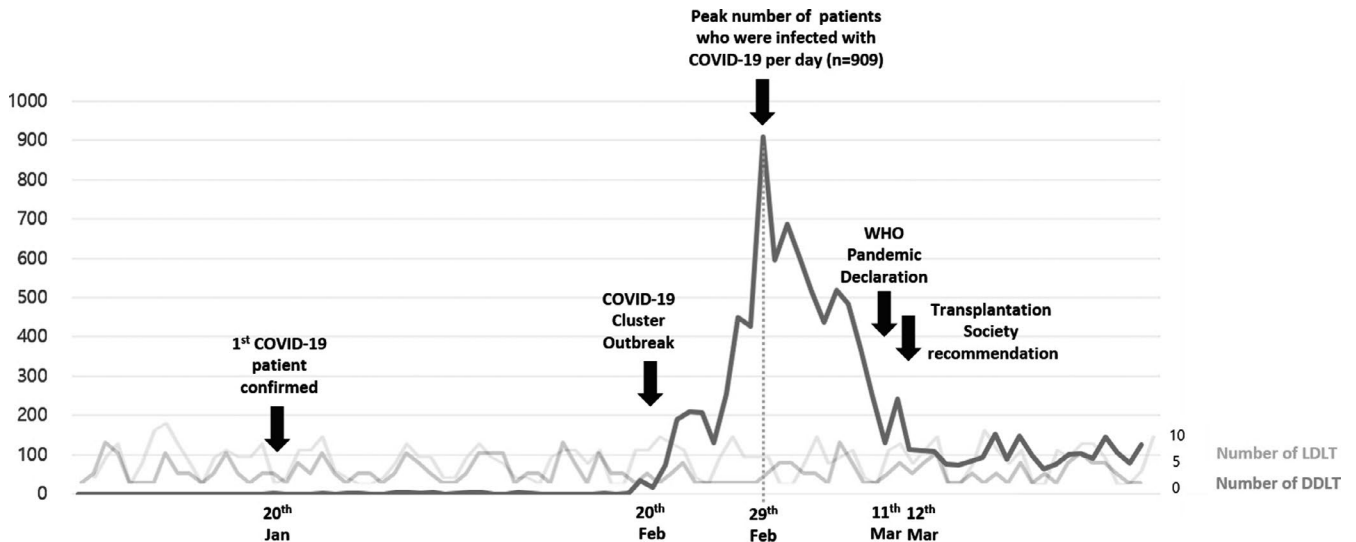
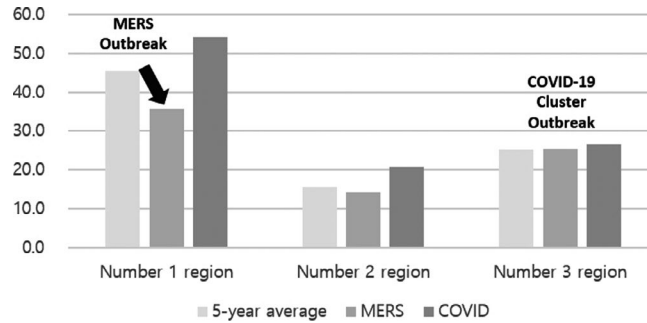


FIGURE 3 The timeline of the relationship between COVID-19 confirmed patients with the number of transplantation

but the total number of cases recovered to the average number of cases observed in the second half of the year. The number of DDLT was constant regardless. During the MERS outbreak, there was a decrease in the total number of cases in the early stage because the

infected patient's location was concentrated in the region where most transplants are usually done. However, COVID-19 massive infection occurred in the region ranked 3rd in the total number of LT performed in Korea. Therefore, the effect on the total number was relatively low.

FIGURE 4 Difference in number of LT by three region between the MERS and COVID outbreak in Korea



4 | DISCUSSION

Contrary to what was expected before the start of the study, COVID-19 did not reduce the number of liver transplants in Korea. The reason for this might be a recent change in the prevention and treatment of infectious diseases after the MERS outbreak in 2015. I discussed several reasons why the number of liver transplants could be done normally with no decreases in the number of LT like during the MERS outbreak period.

4.1 | Awareness of the needs of the Preparation policies for the prevention of epidemic viral diseases after the MERS outbreak

Since 2000, severe acute respiratory syndrome (SARS) has infected 8098 people and killed 774 people in about 29 countries between November 2002 and July 2003 and due to the H1N1 pandemic, from April 2009 to August 2010, 16 226 people in 136 countries had been reported as dead. A preventive policy of viral disease was established after the SARS epidemic period. The budget was established to make a National Quarantine bed for epidemic viral diseases. The Middle East Respiratory Syndrome (MERS) outbreak in 2015 accelerated this policy. MERS was the first epidemic to occur in Saudi Arabia in September 2012, and by October 2016, there were 1843 infected cases and 705 deaths worldwide. With the continued emergence of several high-risk infectious diseases over the last 20 years, every country around the world has established systematic infection control and prevention system to effectively prepare for the risk of an infectious disease outbreak. Especially in Korea, during the MERS outbreak, the failure of the initial infection source control caused a huge outbreak. The number of incidences is the 2nd highest in the world, with 185 infected (10.6% of the world's incidence) and 38 deaths (5.6% of the world's deaths). As a result, the Korean government and people realized the importance of preparation for a viral disease epidemic.¹⁵

4.2 | Securing of National and regional quarantine beds

According to the announcement by the Korean Central Epidemic Control and Prevention (KCDC), the number of quarantine rooms

in preparation for a huge viral outbreak has been gradually increased. Although it still has not reached the current number of infected people, there are 198 beds in 161 national quarantine rooms for the treatment of COVID-19. There are 141 negative pressure isolation single rooms and 20 shared negative pressure rooms with 57 beds. This is a 66% increase compared with 71 rooms and 119 beds arranged before the MERS outbreak. Also, there are 53 regional medical institutions with 158 negative pressure rooms and 189 beds. Furthermore, the law has been changed to provide negative pressure isolation beds for all the medical institutions with more than 300 beds after the MERS outbreak in Korea. There are 778 medical institutions with negative pressure isolation beds and 460 beds in 326 private hospitals that can be operated. In other words, the number of negative pressure beds that can be used as a National quarantine bed is 198, and by adding the remaining 649 negative pressure beds, a total of 847 negative quarantine beds can be used to treat patients with COVID-19 infection. With the expansion of these facilities, a system capable of establishing and managing against infectious diseases within a short period would have played a major role in controlling COVID-19 in its early stages.

4.3 | Rapid diagnosis and accurate information disclosure

Based on the experience of responding to MERS, KCDC has been taking measures to prevent the impact of epidemics. They had been working to develop a method for the diagnosis of COVID-19 before the outbreak of patients in Korea, and as a result, several companies developed an RT-PCR (reverse transcription-polymerase chain reaction) method that gives the disease diagnosis within 6 hours. Also, the rapid diagnosis method of RT-LAMP (Reverse transcription-loop-mediated isothermal amplification) method is currently under development.¹⁶ Besides, unlike the MERS epidemic, the results of epidemiological studies have been disclosed in detail since the outbreak with the first patient. Currently, if someone has contacted confirmed patients of COVID-19 or visited a dangerous area, then the KCDC recommends an RT-PCR diagnostic test if a coronavirus infection is clinically suspected.^{17,18}

However, after the 31st confirmed case in the Daegu region, an unexpected cluster of infection occurred and the government raised

the public health crisis to the highest emergency stage, a “severe stage.” After that, information on the number of infected, dead, and cured people have been distributed by the KCDC via daily reports and all of the information can be checked on the main page of the major portal site used by 74.4% of Korean people for daily web search. Also, according to the government’s instructions, the transplant society’s recommendations were released the day after the WHO announcement of a “pandemic.” The recommendations included the statement that all donor and recipient candidates should undergo a COVID-19 screening test, and negative findings should be confirmed before admission for transplantation. If the test results were delayed like in other countries, the patients could not undergo transplantation and the delay of transplantation may have adversely affected the patients’ outcome after LT. This could be overcome with a faster diagnosis of COVID-19 in Korea.

4.4 | Deceased donor organ shortage

In Korea, the number of deceased donors per million people per year is 3.15, and the number of cases of death per year is very different from that of the Western country, in a 10-33 ratio.¹⁹ Because of this organ shortage, living donor transplantation is the main type of transplantation performed in Korea. The case of deceased organ donations has not changed significantly in the past 5 years. Because of the small number of cases of brain-dead liver, if possible, even a marginal donor liver is attempted to be used for liver transplantation, and even if it has been refused by the first allocated transplant center for other reasons including COVID-related policies, the organ waste is prevented through next-order hospital waiting. As a result, the number of DDLT was similar to the previous year.

Since LDLT is an elective operation, whose schedule could be adjusted, it was not as emergent as a DDLT operation; thus, the number of LDLT cases has decreased in January when there was a strong lockdown due to COVID-19. Besides, the press article about COVID-19 positivity of the donor during the postoperative period in the city in which the pandemic outbreak occurred warned the population and strongly affected the transplantation society and several transplant centers. Against this background, safe management guidelines have been propagated, the number of confirmed cases has reduced, the system for preventing inter-hospital infections, and the strong screening of COVID-19 before surgery has enabled normal LDLT procedures, whose number has remained the same in many centers. This way, the number of transplants could be maintained.

4.5 | Current screening process for procurement along with the KONOS recommendation

A complete blockade will be the best option in the initial outbreak stage, but as the pandemic progresses, we should think about how a transplant surgeon will be able to give a new life to a patient with

a new organ from a deceased donor and proceed with a transplant in a safely controlled environment. The restrictions of transfers between hospitals and of medical staff’s activity, such as restrictions of deceased donor organ procurement and restrictions of donations in specific areas, can be obstacles to transplantation. Before leaving to another hospital for procurement, procurement team checked the donor’s COVID test result first. Then, according to instructions from KONOS and each hospital, members of the procurement team should be checked and get a confirmation in front of the entrance of the hospital by heat sensors screening, checking the identification number, body temperature, and history of visiting other countries within 2 weeks via online immigration system. Also, there was a center that performed a repetitive ID check in front of the elevator, at the entrance of the operating theater, and each operating room before starting procurement.

Korea has the world’s fastest diagnostic technology; therefore, COVID-19 is relatively well-controlled compared with other countries. Of course, the COVID-19 pandemic is still in progress, but the spreading velocity in Korea has decreased and the number of recovered people from COVID-19 is now increasing. Also, Korea has already experienced the MERS pandemic and has been somewhat vaccinated in preparation for the spread of such viral diseases. Since the MERS, the number of isolated beds has been expanded, medical staff has been further educated, and the public has been able to recognize and actively cooperate in the fight of viral diseases.

However, the COVID-19 pandemic is still underway and its progression cannot be predicted beyond the current stage. When the period of increasing the confirmed people, keeping perfect isolation and lockdown are effective. In the 2nd stage, when the increase in the number of confirmed patients began to decrease and turned into a chronic community-acquired infection, it is necessary to define a good safety boundary for reducing the side effects of prolonged lockdown.

The limitation of this study was that it did not show the mortality of recipient candidates on the waiting list. Because the COVID-19 pandemic period is still short, and KONOS data are compiled for deaths annually, it is difficult to obtain a waiting list mortality for a certain period; thus, it was not analyzed in this study. However, it could be predicted indirectly that an increase in the waiting list mortality was not observed because the number of liver transplants did not decrease significantly during this period and there might have been no delays in liver transplant procedures.

We also realized the lack of infectious medicine specialists, epidemiologists, and supporting manpower even after the MERS outbreak. After this outbreak, infectious disease experts should be assigned to university hospitals, and they are managed to operate and take responsibility for designated infectious diseases. We have been working on increasing the number of infectious medicine specialists since the MERS outbreak, but we still lack the number of investigators to handle the epidemic compared with the population number. The United States Centers for Disease Control and Prevention (CDC) addressed that 1.04 public health professionals are needed per 100 000 people to prepare for an epidemic disease outbreak. The appropriate

number of epidemiologists is estimated to be 348 in Korea. However, only 77 epidemiological inspectors belong to the Centers for Disease Control and Prevention; thus, there were difficulties in the prompt and accurate investigations during this pandemic status.

However, the COVID-19 is still in progress and can now be seen as a step beyond the first stage of the first outbreak. In the case of South Korea, where infections occurred in the early stages, it is considered that this stage will shift to the second stage. Rapid screening examination and transparent disclosure need to provide the public with secure boundaries and areas of activity. From a transplant surgeon's point of view, in such a pandemic situation, I am worried about how to safely reduce the patient's mortality. It is important to set up a process to perform a safe liver transplant operation under appropriate control. In Europe and the United States, where the number of confirmed persons and death is increasing rapidly, it is still considered a procedure that requires activity restrictions and regulations. However, as these are expected to move to the 2nd stage over time, the current situation in Korea is considered to be an appropriate model for those countries.

In conclusion, it is important to keep a social distance. However, even in these difficult periods, setting a proper and safe process and proceeding with liver transplantation within a safe boundary has the positive effect of reducing the side effects of lockdown and saving patients' lives. With safe screening and protective systems along with the COVID-19 outbreak improvement, there was no spread nor infection of COVID-19 in the recipients during this period. The final stage of COVID-19, which is prolonged, is the normalization of everyday life and social activity through the expansion of safe boundaries. As a first step, we have to create guidelines to establish an appropriate safety process in the course of liver transplantation and other solid organ transplants along with the COVID-19 outbreak improvement.

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CONFLICTS OF INTEREST

The author has no conflicts of interest to declare.

AUTHOR CONTRIBUTION

Jeong-Moo Lee participated in the writing/review of the paper, design of the work, research design, performance of the research, and data analysis.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Korean Network Organ Sharing upon request. Restrictions apply to the availability of these data, which were used under license for this study. Publicly available data can be found at <https://www.konos.go.kr/konosis/index.jsp>.

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