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Clinical Characteristics and Outcomes of Liver Transplantation Recipients With COVID-19 Pneumonia

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ABSTRACT

Background. We aimed to evaluate the clinical characteristics and outcomes of mild-severe COVID-19 pneumonia cases in liver transplant (LT) recipients.

Methods. Ten LT recipients diagnosed as having COVID-19 pneumonia in a 6-month period in our transplantation center were included. Demographic and medical data of the recipients were retrospectively collected; clinical courses, treatment responses, and outcomes were evaluated.

Results. Ten LT recipients were male, had a median age of 57 years (min-max, 36-69 years; interquartile range [IQR], 13 years), and had right lobe from living donor LT performed in a median of 11 months (min-max, 1-72 months; IQR, 12 months). Five patients had severe pneumonia, and the remaining patients had mild/moderate pneumonia. The most frequent symptoms were fever (90%) and cough (70%). Favipiravir, enoxaparin sodium, and corticosteroid were initiated at the time of the diagnosis; immunosuppressive drug doses were reduced or discontinued in 3 cases. Lymphopenia median: 510/mL (min-max, 90-1400 mL; IQR, 610 mL), increased levels of C-reactive protein median: 4.72 (min-max, 0.31-23.4; IQR, 8.5), and ferritin median: 641 (min-max, 40 to \geq 1650; IQR, 1108) were frequent. Four patients required antibacterial treatments because of emerging bacterial pneumonia and/or sepsis. All patients were hospitalized for a median of 10 days. One patient with sepsis died on the 26th day after intensive care unit admission, and the remaining 9 survived. No further complication was recorded for 1-month follow-up.

Conclusions. Commencing favipiravir, enoxaparin sodium, and corticosteroid treatments; close follow-up of the developing complications; the temporary reduction or cessation of immunosuppression; a multidisciplinary approach; early awareness of the bacterial infections; and the initiation appropriate antibiotic treatments can contribute to success.

IN December 2019, a pneumonia outbreak caused by a novel coronavirus emerged in the Wuhan Region of China. The virus made a global spread within a few months. The virus is transmitted to humans from contact with droplets and microdroplets in the respiratory secretions of infected individuals [1]. The World Health Organization (WHO) declared this outbreak a “pandemic” on March 11, 2020. The International Virus Taxonomy Committee named this coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 2019 (COVID-19). According to the WHO’s data, by January 22, 2021, more than 98 million

confirmed cases of COVID-19 were identified worldwide, and approximately 2.1 million people died [2]. It was observed that the mortality rate of COVID-19 in the general population was 2% to 3%, but the risk of death was higher (>50%) in older

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people and people with underlying diseases, such as chronic lung diseases, cardiovascular diseases, immunosuppression, diabetes, obesity, hypertension, and cancer [3]. Among these, the patients with solid-organ transplants (SOTs) are a particular concern. It has been reported that mild-severe respiratory failure findings developed at a rate of 39.6%, and the mortality rate was 18% in liver transplant (LT) recipients [4].

LT is the second most frequent SOT worldwide after kidney transplant and still the unique treatment choice for the patients with end-stage liver disease [5]. These patients are particularly susceptible to infections because of ongoing immunosuppression, their background with major surgery, and the possible systemic injuries that were potentially developed because of long-standing illness and treatment courses [6]. However, the clinical course, optimal treatment modalities, and outcomes of COVID-19 in LT recipients are not yet known in all aspects [7]. Based on the experiences from 2 previous coronavirus outbreaks, it appeared that the risk of liver damage increased in severe acute respiratory syndrome and Middle Eastern respiratory syndrome diseases [8]. In a recent international cohort, LT recipients hospitalized with a diagnosis of COVID-19 compared with the nontransplant patients had a higher incidence of severe disease (39% vs 6.1%) and higher mortality rates (24% vs 4.3%) [9,10]. Unfortunately, the current data are still very limited, restricting our understanding of the clinical characteristics and outcomes of the LT patients with COVID-19. Because no effective drugs or therapies were available, countries have adopted different preventive and therapeutic strategies against COVID-19 [11]. The Turkish Health Ministry has recommended commencing hydroxychloroquine and/or favipiravir + enoxaparin sodium to all patients with the diagnosis of COVID-19 [12]. In this perspective, the outcomes of the LT recipients who received the treatment mentioned above have not been reported previously in our country.

In the current study, we aimed to evaluate that the clinical characteristics, treatment processes, and outcomes of LT recipients who were hospitalized in our medical center because of COVID-19 pneumonia. The results of this study may also contribute to coping with COVID-19 pneumonia both for the patients with SOT and for people who had no previous health problems.

MATERIALS AND METHODS

Study Design and Patients

This study was conducted in the Liver Transplantation Institute of Inonu University, which is a 130-bed organ transplantation center performing about 200 LTs annually. Patients who underwent LT in our hospital, were admitted to our center with the diagnosis of COVID-19, and were followed up in the intensive care unit (ICU) because of COVID-related pneumonia between March and October 2020 were included in this study. However, patients who underwent LT in our center, were diagnosed as having COVID-19, and were followed up in other centers were excluded in the study. A retrospective data screening in the hospital registration system revealed that 10 LT patients were diagnosed as having COVID-19-related pneumonia in the facility since the emergence of the SARS-CoV-2 pandemic. The information related to the medical status of these patients, including demographic characteristics,

clinical data (onset symptoms, treatments administered, results of the laboratory tests and radiological imaging, and clinical progressions), and the outcomes were collected.

Definitions

The diagnosis of COVID-19 pneumonia was established according to the “COVID-19 Diagnosis and Treatment Guidelines of the Turkish Health Ministry” [12]. The criteria of mild/moderate pneumonia were as follows: respiratory rate <30/min and oxygen saturation as measured by pulse oximetry (SpO₂) >90% in room air and <50% lung involvement in the radiograph film of the chest or thoracic computed tomography (CT). Severe pneumonia criteria were as follows: respiratory rate ≥30/min or dyspnea, SpO₂ ≤90% or PaO₂/fraction of inspired oxygen ≤300 mm Hg, respiratory failure requiring mechanical ventilation, shock or failure of other organs requiring ICU monitoring, new multilobar lesions on lung imaging or progression >50% in existing lesions within 48 hours, sequential organ failure assessment score ≥2, and concomitant pneumothorax. Outcomes of the patients were assessed with recovery or 30-day all-cause mortality. The definition of the recovery from COVID-19 pneumoniae was based on the “SARS-CoV-2 Diagnosis and Treatment Guidelines of the Turkish Health Ministry” with minor modifications [12]. The cases were grouped as mild/moderate and severe pneumonia according to the “COVID-19 Severe Pneumonia, ARDS, Sepsis and Septic Shock Management Guideline” [13]. Briefly, resolutions of the clinical symptoms, normalization of blood and serum parameters, SpO₂ ≥95% in normal breathing without any oxygen support, and 2 negative SARS-CoV-2 reverse transcriptase–polymerase chain reaction (PCR) test results obtained at the interval of 2 consecutive days. Thirty-day all-cause mortality was defined as death due to any cause within 30 days of the COVID-19 symptoms onset.

Diagnostic Methods: Laboratory and Imaging

Real-time PCR for SARS-CoV-2 detection. The nasopharyngeal samples of the patients were collected with sterile swabs flocked with medical grade nylon microfibers and placed in vNAT Transfer Tube (Bioeksen R&D Technologies Ltd, Istanbul, Turkey) containing 2 mL vNAT solution, which was manufactured according to DNA/RNA shield technology. After RNA extraction, reverse transcriptase–quantitative PCR (RT-qPCR) was administered using Bio-Speedy SARS-CoV-2 RT-qPCR kit (Bioeksen R&D Technologies Ltd) in the Rotor-Gene Q device (Qiagen; Hilden, Germany). The RT-qPCR kit used in this study was targeting 2 genomic regions of SARS-CoV-2 encoding nucleocapsid protein and ORF1ab.

Blood and serum parameters. Complete blood count (hemoglobin, total white blood cells, and the counts of neutrophils, lymphocytes, and platelets), coagulation parameters (international normalized ratio, D-dimer), acute-phase reactants (C-reactive protein [CRP], Procalcitonin [PCT], interleukin [IL] 6, ferritin), and serum biochemistry values (creatinine, albumin, total bilirubin, lactate dehydrogenase, liver enzymes) were measured initially on the day of COVID-19 diagnosis, as well as throughout the clinical course. In case of clinical suspicion for bacterial infection, sputum, tracheal aspirate, blood, and urine samples were collected for culture and gram staining.

Radiologic imaging. The lung involvement of the LT recipients infected by SARS-CoV-2 was assessed using the chest radiography film and noncontrast thoracic CT scanning. All imaging procedures were performed on a 16-section multidetector CT device (Somatom-Scope, Siemens, Erlangen, Germany). Then, the obtained images were evaluated by author Yalcinsoy.

Data Analysis

Categorical variables were expressed as frequency and percentage, and continuous variables of the patients were expressed as median, minimum-maximum, and interquartile range (IQR).

RESULTS

In this study, 10 LT recipients with a median age of 57 years (min-max, 36-69 years; IQR, 13 years) were analyzed. All patients were male and had right lobe living donor LT in our transplantation center within a median of 11 months (min-max, 1-72 months; IQR, 12 months). The patients had LT because of various reasons, such as chronic hepatitis B virus infection, hepatocellular carcinoma, and sclerosing cholangitis. All patients were receiving immune suppressive treatment with tacrolimus and mycophenolate mofetil (90%) or everolimus (10%). Diabetes mellitus was the most common comorbidity.

At initial evaluation, 4 of the studied recipients were manifesting severe pneumonia, and another recipient progressed to severe pneumonia during the hospitalization course. The representative CT images of the patients are shown in Fig. 1, 2, and 3.

The most frequent COVID-19 onset symptoms were fever (90%), cough (70%), fatigue (70%), and dyspnea (60%). Favipiravir (1600 mg daily twice on the first day; after then, 600 mg

daily twice for minimum 4 days) for 5 to 10 days, enoxaparin sodium (0.6 mg daily once), and methylprednisolone (40-250 mg/d) or dexamethasone (6-8 mg/d) were initiated as soon as possible to the patients. All recipients were hospitalized for a median of 10 days (min-max, 5-32 days; IQR, 11 days). Three patients with severe pneumonia required ICU stay for a mean of 17 days and mechanical ventilation for a mean of 8 days. According to the clinical courses, 3 patients received an IL-6 receptor blocker, tocilizumab (8 mg/kg max 800 mg, only once or twice). Four patients with severe pneumonia developed bacterial infections, including sepsis ($n = 3$) and pneumonia ($n = 1$). After antibacterial treatment, 3 of these patients recovered, but the remaining 1 patient died. No further progression was recorded in other patients studied. Overall, 9 of the patients fully recovered from COVID-19 pneumonia (30-day all-cause mortality was 10%). General characteristics of the patients related to LT and COVID-19 pneumonia are shown in Table 1.

At the initial evaluation, 5 patients presented with low blood leukocytes level ($<2.65 \times 10^3/\text{mL}$), 5 with low lymphocytes level ($<600 \times 10^3/\mu\text{L}$), 7 with high CRP ($>9 \text{ mg/dL}$), 4 with high IL-6 ($>100 \text{ pg/mL}$), and 4 with high ferritin ($>1000 \text{ ng/mL}$) levels. The international normalized ratio and D-dimer results were also indicative of intravascular coagulation. During the clinical course, these parameters worsened further. The liver enzymes of 9 of the patients were detected in normal ranges. The blood and serum test results of the patients are shown in Table 2.

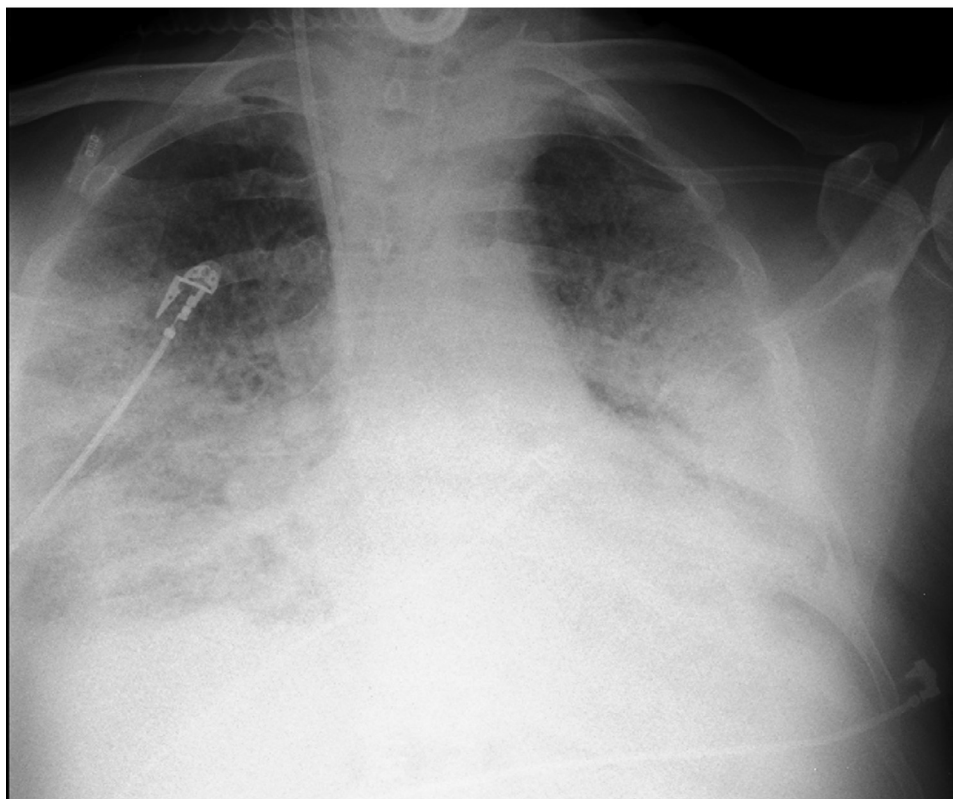


Fig 1. Posterior-anterior chest radiography. Moderate to severe pneumonia with bilateral diffuse infiltration.



Fig 2. Moderate to severe coronavirus disease 2019 pneumonia thoracic computed tomography image. Diffuse ground glass image (thick black arrow) and infiltration (black arrow) with air bronchogram on.

DISCUSSION

In this study, we evaluated the clinical characteristics of COVID-19 pneumonia cases with LT, a group of patients having high risk for the serious health problems such as organ rejection or death because of a developing infection. To our knowledge, this is the first study involving such a group of patients from Turkey applying a particular antiviral and anticoagulant treatment policy all over the country. Although 1 of our patients died, 9 of our patients recovered. The patients were closely followed up with the specialists from infectious diseases, chest diseases, intensive care, and general surgery.

In an epidemiologic study that included SARS-CoV-2–positive persons, it was reported that 29.2% of the patients showed neither any clinical symptom nor any positive radiologic image in thoracic CT [14]. The high frequencies of severe pneumonia and mortality rate were reported from the patients of older ages, male sex, chronic obstructive pulmonary disease, cardiac failure, diabetes mellitus, renal disease, hematologic malignancy, and SOT [15]. However, there are still many unknowns as to why some individuals with no comorbidity die or have severe pneumonia because of COVID-19 and why other individuals with multiple known medical predisposing factors recover from this infection. Although varying by country and territory, 2.2% of the infected patients across the world lost their life because of SARS-CoV-2 according to the WHO’s database by January 22, 2021 [16]. Therefore, investigation of the clinical features

and outcomes of special patient groups can substantially enlighten the dynamics of COVID-19. Additionally, evaluating the patients’ clinical characteristics who received different treatment regimens will also help determine optimal management strategies [17]. In SOT recipients, because of increased angiotensin-converting enzyme 2 protein expression and intense immunosuppression, COVID-19 is more likely to occur within the early period after LT (especially in the first 6 months) [18]. According to current knowledge, COVID-19 that develops in LT recipients is more severe and has higher mortality rates than in individuals who have not undergone LT, but the data are still very limited [19]. In a multicenter study that included 10 renal transplant patients who were found positive for SARS-CoV-2, Nair et al [20] reported that 7 patients (70%) developed pneumonia, 3 patients (30%) died, and half of the patients developed acute kidney injury. In a nationwide study from France that included 279 renal transplant patients diagnosed as having COVID-19, 46% of the patients developed severe pneumonia, and about 23% of all the studied patients died within 30 days [21]. In another multicenter study that included more than 480 SARS-CoV-2–positive patients with kidney, pancreas, liver, heart, and lung transplants, Kates et al [22] reported that 31% of the patients required mechanical ventilation, and 20.5% of patients died. The immunosuppressive treatments of the patients in that study were modified after the diagnosis of COVID-19. The patients were administered different antiviral drugs, corticosteroids, and immunomodulators such as anti-IL-6 drugs

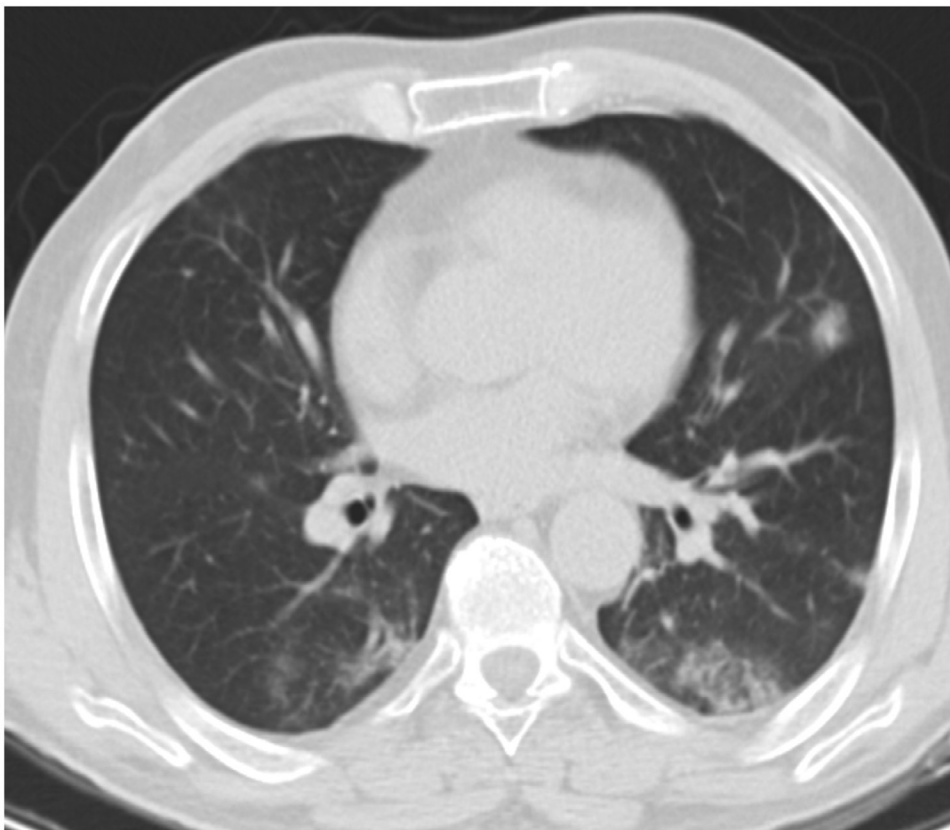


Fig 3. Mild coronavirus disease 2019 pneumonia thoracic computed tomography image/

and/or convalescent plasma and intravenous immunoglobulin. Additionally, the authors underlined that specific predisposing factors, such as congestive heart failure, chronic lung disease, and obesity, were independently associated with mortality. Webb et al [23] conducted a cohort study with 28 LT recipients and 167 individuals in the control group. According to that study, the mortality rate of the LT recipient group (19%) was lower than the control group (27%). No deaths were liver related in the transplant group. In this cohort study, 6 of the 8 patients (75%) with nonliver cancer died, among whom the causes of death were COVID-19 lung disease 4 (67%), cardiac related (17%), and multiorgan failure (17%).

We observed that most of our patients presented common COVID-19 lung involvement onset symptoms, such as fever, dry cough, and dyspnea. Two patients also presented with muscle and joint pains, and 1 had gastrointestinal symptoms. Fever was the most frequent symptom in our patients, generally mild-moderate (37.8°C - 38.7°C). In a study conducted by Pereria et al [18], which included 90 SOT patients in 2 centers in the United States, the most common symptoms were fever, cough, and dyspnea, similar to the general population, and dyspnea was reported to be the most important finding for severe clinical course. Measurement of D-dimer, ferritin, PCT, CRP, IL-6,

and high-sensitive troponin is initially valuable in hospitalized patients. Lymphopenia is a common laboratory finding. An increase in D-dimer, progressive lymphopenia, and inflammation parameters are more likely in severe and critically ill patients [24]. In our LT recipients, all presented with anemia, which was one of the common findings in LT patients. On the other hand, we detected low blood leukocyte number, lymphopenia, high CRP levels, PCT, and ferritin in our patients on the diagnosis day of COVID-19 and throughout its clinical course. These findings during the initial evaluation were similarly observed in a non-LT population. However, more care should be taken in LT recipients concerning nephrotoxic and hepatotoxic adverse effects of drugs used for the treatment of COVID-19 and their interactions with immunosuppressive drugs used.

Radiologically, the sensitivity of noncontrast thoracic CT to detect infiltrations in the lung parenchyma in the early period is higher than posterior-anterior chest radiography. When the diagnosis of COVID-19 pneumonia is made in the SOT patient group, it should be kept in mind that bacterial pneumonia may accompany both at the time of diagnosis and during follow-up [25]. We evaluated the clinical courses of 10 LT recipients with mild/moderate to severe COVID-19 pneumonia. During our treatment courses of COVID-19 pneumonia, 3 patients in the ICU (all sepsis) and 1 patient (severe pneumonia) in the clinic

Table 1. Demographic and Clinical Characteristics of the Patients and Outcomes

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age, y	56	36	64	51	57	40	69	65	57	59
Cause of LT	Alcoholism	Wilson disease	HBV + HCC	Sclerosing cholangitis	HBV + HCC	HBV	HBV + HDV	Cryptogenic liver disease	Neuroendocrine tumor	Sclerosing cholangitis
Immunosuppressive drug (s) for LT	TAC, MMF, prednol	TAC, MMF, prednol	TAC, MMF, prednol	TAC, MMF	TAC, MMF	TAC, MMF, prednol	TAC, MMF	TAC, MMF	EVO	TAC, MMF
Time to COVID-19 diagnosis after LT, mo	1	6	5	7	17	4	72	23	15	15
Beginning symptoms	Fever, dyspnea, cough	Fever, dyspnea, abdominal pain, nausea, vomiting	Fever, cough	Nausea, muscle/joint pain	Fever, weakness	Fever, weakness, muscle pain	Fever, dyspnea, cough	Fever, dyspnea, cough	Fever, dyspnea, cough	Fever, dyspnea, cough
Comorbidity	-	DM, liver abscess	HT	-	DM	-	DM	-	DM	Asthma, atrial fibrillation
Length of favipiravir treatment, d	10	10	10	10	8	5	10	10	10	10
Grade of pneumonia	Severe	Severe	Severe	Severe	Mild/moderate	Mild/moderate	Mild/moderate	Mild/moderate	Severe	Mild/moderate
Corticosteroid, mg/d	Prednol 250	Methylprednisolon 80	Methylprednisolon 250	Methylprednisolon 80	Methylprednisolon 80	Methylprednisolon 40	Dexamethasone 6	Prednol 80	Prednol 80	Prednol 80
Length of treatment, d	3	10	3	5	5	5	10	5	10	10
Additional drug for COVID-19	Tocilizumab	-	Tocilizumab	-	-	-	-	-	-	-
Infection and pathogen	Sepsis <i>Klebsiella pneumoniae</i> ESBL (+)	Sepsis <i>K. pneumoniae</i> ESBL (+)	Sepsis	Pneumonia	-	-	-	-	-	-
Antibacterial administered	MER, LINZ, ANI	MER, TIG	MER, LINZ	SAM, CLR	-	-	-	-	-	-
Length of antimicrobial treatment, d	17	14	14	7	-	-	-	-	-	-
Hospital stay, d	26	32	21	10	8	5	10	10	10	10
ICU stay, d	26	18	8	-	-	-	-	-	-	-
MV, d	12	7	5	-	-	-	-	-	-	-
Total outcome	Death	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery	Recovery

ANI, anidulafungin; CLR, clarithromycin; DM, diabetes mellitus; ESBL, extended-spectrum beta-lactamase; EVO, everolimus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HT, hypertension; ICU, intensive care unit; LT, liver transplant; LINZ, linezolid; MER, meropenem; MMF, mycophenolate mofetil; MV: mechanical ventilation; SAM, ampicillin/sulbactam; TAC, tacrolimus; TIG, tigecycline.

Table 2. Blood and Serum Parameters of the Studied LT Patients During the Clinical Course of COVID-19

Test Parameters	Throughout Hospitalization			Normal Ranges of the Parameters	
	Median	Min-Max	IQR	Min	Max
Hemoglobin, g/dL	9.85	(7.1-14.1)	3.4	13.6	17.2
Total WBC, 10 ³ /μL	5.31	(1.49-18.1)	4.17	4.3	10.3
Neutrophil, 10 ³ /μL	4.05	(1.36-16.5)	3.4	2.1	6.1
Lymphocyte, 10 ³ /μL	510	(90-1400)	610	1.3	3.5
Platelet, 10 ³ /μL	75	(11-250)	68	156	373
INR	1.1	(0.9-2.49)	0.29	0.8	1.2
D-dimer, mg/L	1.78	(0.3-33.55)	4.27	0	0.55
CRP, mg/dL	4.72	(0.31-23.4)	8.5	0	0.351
PCT, ng/mL	0.55	(0.02-44.7)	1.77	0	0.05
IL-6, pg/mL	39	(4.3-843)	104.2	0	7
Ferritin, mg/mL	641	(40-≥1650)	1108	22	322
Creatinine, mg/dL	1.06	(0.4-2.76)	0.4	0.72	1.25
Albumin, g/dL	2.8	(1.6-4)	0.6	3.4	4.8
Total bilirubin (mg/dL)	0.85	(0.14-7)	1.91	0.2	1.2
LDH, IU/mL	255	(112-1125)	223	125	243
ALT, IU/L	34	(9-347)	35	0	35
AST, IU/L	28	(12-127)	29	5	34

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; IL, interleukin; INR, international normalized ratio; IQR, interquartile range; LDH, lactate dehydrogenase; PCT, procalcitonin; WBC, white blood cell.

developed a bacterial infection. Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* grew in the blood samples of 2 patients with sepsis, but no pathogen was detected in the other 2 patients. Three of these patients responded well to the antibacterial treatment, but 1 patient who had LT recently could not be saved.

The Centers for Disease Control and Prevention Clinical Guidance for Management of Patients with Confirmed COVID-19 Disease (as of November 3, 2020) states that no specific treatment is available [26]. However, more than 300 active clinical therapy trials are in progress. In these studies, chloroquine-hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, corticosteroids, and adjunctive therapies (anticytokine or immunomodulatory agents and immunoglobulin therapy) have been administered to patients [27]. No high-quality evidence exists for the efficacy of chloroquine/hydroxychloroquine therapies for SARS-Middle Eastern respiratory syndrome [28]. Tocilizumab, a monoclonal antibody IL-6 receptor antagonistic, has been used in a small series of severe COVID-19 cases [29]. Other potential adjunctive therapies are convalescent plasma or hyperimmune immunoglobulins that antibodies from recovered patients may help with both free virus and infected cell immune clearance for COVID-19 treatment [30]. The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and acute respiratory distress syndrome [31]. It is likely that the beneficial effects of corticosteroids in severe viral respiratory infections are dependent on a selection of the right dose at the right time and in the right patient. However, this benefit may be outweighed by adverse effects, including delayed viral clearance and increased risk of secondary infection [32]. Therefore, successful and balanced suppression of systemic anti-

inflammatory response in COVID-19 pneumonia can be life-saving. All these data indicate that the clinical courses and the outcomes of COVID-19 in SOT recipients are influenced by a high number of factors belonging to the patients' medical characteristics; medical standards of the countries and the treatment regimens are administered [33]. Therefore, the need for data from this specific patient group sharing similar characteristics is occurring for better planning the treatment modalities for COVID-19 in not only LT recipients but also in other patients [34]. In the early period of the COVID-19 diagnosis, favipiravir, enoxaparin sodium as an anticoagulant drug, and methylprednisolone (40-250 mg/d) or dexamethasone (6-8 mg/d) were administered to all of our recipients. Oxygen support given through nasal cannula improved blood oxygen saturation (>90%) in 9 patients, but a patient who had LT 25 days ago required endotracheal intubation in the ICU. During the clinical follow-up, 2 more patients with severe COVID-19 pneumonia showed a progressive decrease in the blood oxygen saturation and required mechanical ventilation in ICU. However, that patient had a high number of comorbidities; for example, he had major surgery (LT) in the last month and was still in the intensive immunosuppression and ICU stay. His medical condition and self-care were already rather poor at the pre-LT period because of long-standing chronic alcoholism. Furthermore, he had additional immunosuppression because of COVID-19, such as high-dose corticosteroid and tocilizumab; then he developed sepsis because of an extended-spectrum beta-lactamase (+) *K pneumoniae*, which is a highly fatal complication even in nontransplant patients.

To our knowledge, this is the first study in Turkey reporting the clinical characteristics of LT patients diagnosed as having COVID-19 pneumonia. Although there was also a 10% mortality rate in our patients, we found that 4 patients with severe and

5 patients with mild/moderate COVID-19 pneumonia survived. Although our patients had risk factors (such as major surgery, advanced age, immunosuppression, male sex, and diabetes mellitus) for high mortality in COVID-19 pneumonia, only 1 of our patients died. This mortality rate (10%) was lower than the rates previously reported.

Limitations

In this study, we evaluated 10 LT patients with mild/moderate and severe pneumonia due to SARS-CoV-2. This number was the sum of all the LT recipients for 8 months in our facility. Although it would be better to investigate higher numbers of the patients to analyze the clinical outcomes, no other patients could be found during the study period. We thought that the awareness of the LT recipients about their critical health status and obeying the public measurements, such as mask wearing, social distancing, etc, could prevent the spread of pandemic.

CONCLUSIONS

Given that it has a lower mortality rate value than reported in previous studies, we speculate that commencing favipiravir, enoxaparin sodium, and corticosteroid treatments; close follow-up of the developing complications; temporary reduction or cessation of immunosuppression; a multidisciplinary approach; early awareness of the bacterial infections; and the initiation of appropriate antibiotic treatments contributed to this success. Because we observed a mortality rate in our LT patients as very close to the non-LT population with COVID-19 pneumonia, we believe that some aspects of the data we present in this study have the potential to contribute to the ongoing battle against COVID-19 pneumonia in a non-LT population as well. However, comprehensive multicenter studies on COVID-19 pneumonia with large numbers of LT recipients are needed to clarify the efficacy, adverse effect potential, and drug interactions of existing drugs in this patient group.

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REFERENCES

[1] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270–3.

[2] World Health Organization. World Health Organization coronavirus disease (COVID-19) situation dashboard. < <https://covid19.who.int> > [accessed 21.01.10].

[3] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with

COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.

[4] Colmenero J, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021;74:148–55.

[5] Metin O, Simsek C, Gurakar A. Update on liver transplantation-newer aspects. *Turk J Med Sci* 2020;50:1642–50.

[6] Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol* 2020;5:532–3.

[7] Liu H, He X, Wang Y, et al. Management of COVID-19 in patients after liver transplantation: Beijing working party for liver transplantation. *Hepatol Int* 2020;14:432–6.

[8] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382:727–33.

[9] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382:1708–20.

[10] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang L, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061.

[11] Hongzhou Lu. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *BioScience Trends* 2020;14:69–71.

[12] The Republic of Turkey Ministry of Health. COVID-19 (SARS-CoV-2 infection) (Study of Scientific Board) < <https://covid19bilgi.saglik.gov.tr/Tr/Covid-19-RehberI.html> > [Accessed 30.05.2020].

[13] Vatansver S, Tekin EA, Gultop F, Uğurlu F, Mıngır T, Okur O, et al. COVID-19 patient management in intensive care. *Eur Arch Med Res* 2020;36(Suppl. 1):34–42.

[14] Hu Z, Song C, Xu C, Jin G, Chen Y, Xu X, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Sci China Life Sci* 2020;63:706–11.

[15] Suárez JG, et al. Impact of hematologic malignancy and type of cancer therapy on COVID-19 severity and mortality: lessons from a large population-based registry study. *J Hematol Oncol* 2020;13:133.

[16] World Health Organization. WHO coronavirus disease (COVID-19) dashboard. < <https://covid19.who.int/> > [accessed 30.05.2021].

[17] Gasmi A, Noor S, Tippairote T, Dadar M, Menzel A, Björklund G. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. *Clin Immunol* 2020;215:108409.

[18] Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. *Am J Transplant* 2020;20:1800–8.

[19] Sahin TT, Akbulut S, Yilmaz S. COVID-19 pandemic: its impact on liver disease and liver transplantation. *World J Gastroenterol* 2020;26:2987–99.

[20] Nair V, Jandovitz N, Hirsch JS, Nair G, Abate M, Bhaskaran M, et al. COVID-19 in kidney transplant recipients. *Am J Transplant* 2020;20:1819–25.

[21] Caillaud S, Anglicheau D, Matignon M, Durrbach A, Greze C, Frimat L, et al. An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants. *Kidney Int* 2020;98:1549–58.

[22] Kates OS, Haydel BM, Florman SS, Rana MM, Chaudhry ZS, Ramesh MS, et al. COVID-19 in solid organ transplant: a multi-center cohort study [e-pub ahead of print]. *Clin Infect Dis* doi:10.1093/cid/ciaa1097, accessed May, 30, 2020.

[23] Webb GJ, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, et al. Outcomes following SARS-CoV-2 infection in liver

transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol* 2020;5:1008–16.

[24] Kermalia M, Khalsaa RK, Pillaia K, Ismaila Z, Harky A. The role of biomarkers in diagnosis of COVID-19 – a systematic review. *Life Sci* 2020;254:117788.

[25] Farias LPG, Fonseca EKUN, Strabelli DG, Loureiro BMC, Neves YCS, Rodrigues TP, et al. Imaging findings in COVID-19 pneumonia. *Clinics (Sao Paulo)* 2020;75:e2027.

[26] Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) clinical care. < <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html> >[accessed 30.05.2020].

[27] Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA* 2020;323:1824–36.

[28] Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L, et al. [A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19]. *Zhejiang Da Xue Xue Bao Yi Xue Ban* 2020;49:215–9 [in Chinese].

[29] Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A* 2020;117:10970–5.

[30] Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis* 2020;20:398–400.

[31] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* 2020;395:473–5.

[32] RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with COVID-19 - preliminary report. *N Engl J Med* 2021;384:693–704.

[33] Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res* 2020;7:4.

[34] Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7). *Chin Med J (Engl)* 2020;133:1087–95.