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Outcomes of COVID-19 in Liver Transplant Recipients: A Single Center Experience

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1. Abstract

1.1. Aim: COVID-19 pandemia has a significant negative influence on liver transplantation. The transplantation centers has used different managment protocols to overcome this public health concern. Data about COVID-19 in liver transplant recipients bases on limited availability of studies. We reported herein our institutional experience to contribute collecting data to achieve more precise conclusions.

1.2. Methods: The patients were diagnosed COVID-19, if the result of reverse transcriptase polymerase chain reaction assay was positive and/or there were typical findings at computed tomography. The demographic features of patients, the type of symptoms, the laboratory findings and outcomes of the patients were recorded.

1.3. Results: Totally, 242 patients were enrolled into the study: 212 patients who underwent LT before the pandemia and 32 patients who were carried out liver transplantation during the pandemia. 30 patients contracted COVID-19 during the study period (30/242, 12.3%). Of these 30 patients, 11 patients (36.7%) were hospitalized. The proportion of intensive care unit admission was 23.3% (7/30). The mortality rate was 13.3%. The factors significantly associated with death were increased level of CRP and AST and the degree of lymphopenia at the time of diagnosis.

1.4. Conclusion: In our monocentric study, an exact recommendation was not obtained. The purpose of the transplant centers should be overcoming the region spesific challenges for liver transplantation in the light of recommendations of the major international hepatology societies.

2. Introduction

Since coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus 2 has been regarded as pandemia in March 2020, liver transplantation (LT) programmes has also considerably been affected worldwide [1]. In related to unknown features of COVID-19, the decision of performing LT was controversial at the beginning of the pandemia.

COVID-19 has different clinical presentation from asymtomatic patient to development of multi-organ failure and estimated mortality rate is 2-5% in general population. The patients with older age and chronic diseases such as diabetes mellitus (DM), hypertension (HT) and chronic obsructive pulmonary disease (COPD) are considered as high risk patients with increased mortality rates. Based on this, the patients following LT are clearly in high risk group in addition to immunosupressive condition [2].

Obviously, most of the transplantation centers has suspended to carry out LT in the early days of pandemia. In time, it has been noted that the clinical manifestations of COVID-19 in patients following LT was not significantly different from general population [3]. Even though there was limited data about transplant recipients with COVID-19, some suggestions ground on expert consensus stated that LT surgery could be perform after careful risk assessments [4, 5]. Because, a considerable amount patients with end stage liver disease might not have enough time until the pandemia is over.

This report presents our single center experience in the management and outcomes of 30 liver transplant recipients with COVID-19.

3. Materials and Methods

This retrospective study was approved by the Instutional Clinical Research Ethics Committee (decision no: 2021-09/70). We have performed 464 LT between March 2012 and November 2020. The liver transplant patients who had follow-up visits between March 1, 2020 and November 30, 2020 and the patients who were performed LT in the same period were included in our study to reach admissible follow-up time. Transplant recipients obtain periodic follow-up at our department of transplantation. During pandemia, control interval of patients was prolonged in order to prevent the risk of contamination.

The patients were diagnosed COVID-19, if the result of reverse transcriptase polymerase chain reaction assay (RT-PCR) was positive and/or there were typical findings at low-dose chest computed tomography (CT). The demographic features of patients including age, gender, body mass index (BMI), etiology of primary disease, the type of symptoms and the interval between LT and COVID-19 were recorded. Besides, lymphocyte, ferritin, D-dimer and C - reactive protein (CRP) levels of patients were also recorded.

The COVID-19 diagnosed patients were divided into two groups in related to the severity of symptoms. The patients with mild to moderate clinical condition were followed at home. The patients with severe symptoms in need of standard /high- flow nasal oxygen therapy or non-invasive continuous positive airway pressure (CPAP) or mechanic ventilation were hospitalized.

A special squad consist of an infectious diseases physician and a pulmonologist has made the decision of hospitalization and has also managed the treatment of COVID-19.

3.1. Management of immunosuppressive therapy

Our standard immunosuppressive regimen consists of calcineurin inhibitors (CNI), anti-metabolites and corticosteroids (CS). LT recipients receive triple immunosuppression in the first three months. We minimize the CS dose on the purpose of withdrawal in the third month of LT. We discontinue anti-metabolites after the sixth month of surgery. We routinely switch CNI to mammalian target of rapamycin inhibitor (mTORI) in the patients with hepatocellular carcinoma beyond Milan criteria at the sixth month following LT. We have arranged the immunosuppressive therapy of patients considering the severity of COVID-19. In patients who were followed at home, the anti-metabolite was discontinued and the dose of CNI/mTORI was decreased by half. CS was continued at the dosage they used. CNI/mTORI dosage was increased to initial dosage after the relief of symptoms. However, using the anti-metabolite was started following the negative result of RT-PCR assay.

In hospitalized patients, the management strategy of immunosuppression was the withdrawal of CNI/mTORI and anti-metabolite. Dexamethasone (10mg/day) or methyl prednisolone (1mg/kg/day) treatment was applied in this group during the course of hospitalization. Following discharge, the patients started using CNI/mTORI by half of dosage they have used before COVID-19.

3.2. Management of COVID-19 Therapy

The main treatment against COVID-19 in non-hospitalized patients was favipiravir and all nine-teen patients have used this antiviral drug. Additionally, three patients have used hydroxychloroquine. All patients were under anticoagulant therapy with low molecular weight heparin (LMWH) to prevent thromboembolic complications and continued until the COVID-19 tests were negative or until symptoms had resolved. None of them used antibiotics.

In hospitalized group, antiviral therapy consisted of favipiravir, ganciclovir and remdesevir in eight patients, two patients and one patient, respectively. Only two hospitalized patients have received hydroxychloroquine. However, all patients in this group needed broad spectrum antibiotics due to super/coinfection. These patients have also received LMWH therapy similar to non-hospitalized patients. Standard and high flow nasal oxygen support was the first line therapy for this group. The patients who needed CPAP or mechanic ventilation were admitted to intensive care unit (ICU).

3.3. Statistical Analysis

Statistical analyses were done with Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical data are presented as counts and percentages. The distribution of variables was controlled by Shapiro-Wilk test. Variables showing an association with normal distribution were reported as mean±standard deviations and to compare the mean between two independent group unpaired t test was used. Non-normally distributed variables were presented as median (minimum/maximum) values and Mann-Whitney U test was used to compare differences between two independent groups. Categorical variables were presented with frequency and percentage (n (%)) and were compared using Fisher's exact chi-square test. P-values less than 0.05 were considered statistically significant.

4. Results

The first COVID-19 case was reported on March 11, 2020 in our country. Between March 1, and November 30, 2020, 32 patients were performed LT in our center during pandemia. Eighteen patients underwent deceased donor LT (56.3%). Of these 32 patients, 6 patients (18.8%) contracted COVID-19. Only one patient contracted COVID-19 during early postoperative period, at fifth day following LT. The other five patients contracted COVID-19 disease after discharge, between one and ten months following LT. Of these 6 patients, only one patient who contracted COVID-19 ten months after LT died (1/32, 3.1%).

In the study period, 212 transplant recipients who were performed LT before pandemia were examined at our outpatient clinic and emergency department. Twenty-four patients among these LT recipients (24/212, 11.3%) suffered COVID-19. Of these 24 patients, 3 patients died (12.5%) due to COVID-19.

Totally, 242 patients were enrolled into the study: 212 patients who

underwent LT before the pandemia and 32 patients who were carried out LT during the pandemia. 30 patients contracted COVID-19 during the study period (30/242, 12.3%). There were 19 (63.3%) and 11 (36.7%) patients in the Group 1 and the Group 2, respectively. The median age was 64.5 years (43-74). The proportion of male patients was higher than female patients (20, 66.7%). The most common etiological cause was Hepatitis B virus (11/30, 36.7%). All of these patients had functional graft with normal liver function tests before COVID-19. RT-PCR assay was positive in all patients. The typical thorax CT findings was detected in all patients belonging to the Group 2 (11/30, 36.7%), but none of the patients in the Group 1 has CT findings. Fever (47.3%), coughing (47.3%) and myalgia (47.3%) were most seen symptoms in the Group 1. The patients in the Group 2 had similar frequency of symptoms of fever, coughing and myalgia. Besides, the hospitalized patients have additionally suffered shortness of breath (8/11, 72.7%). All hospitalized patients were isolated and treated in the COVID-19 unit.

The mean follow-up time was 7.5 months (5-11). Hospitalization was not necessary in Group 1 in the course of disease. None of the patients has experienced graft rejection during the COVID-19 treatment. Liver enzymes increased as three times of normal values in three patients who were hospitalised. The liver function was normal in these patients at the discharge.

CPAP and mechanic ventilation support was required in two and five patients in Group 2, respectively. The proportion of ICU admission was 23.3% (7/30). None of the hospitalized patients were still in ICU at last follow-up. Of five patients who needed mechanic ventilation, four patients died due to multi organ failure (4/30, 13.3%). There were no liver related deaths.

The influence of the general characteristics, and the laboratory findings on mortality were compared between the patients who died and the recovering patients. Most common comorbidities included overweight (80%), diabetes (50%), hypertension (16.7%), chronic renal failure (13.3%), respiratory disease (6.6%) and cardiovascular disease (3.3%). By contraries, the presence of comorbidities was not associated with mortality (Table 1). The factors significantly associated with death were increased level of CRP and AST and the degree of lymphopenia at the time of diagnosis (Table 2).

Table 1: Risk factors for mortality (comorbidities)

	Survived (n=26)	Died (n=4)	P value
Diabetes mellitus	11, 42.3%	4, 100%	0,100
Hypertension	4, 15.4%	1, 25%	0,538
Respiratory disease	1, 3.8%	1, 25%	0,253
Cardiovascular disease	1, 3.8%	none	0,999
Chronic renal failure	3, 11.5%	1, 25%	0,454

Table 2: Risk factors for mortality (baseline and admission features)

	Survived (n=26)	Died (n=4)	P value
Age	64,5(43-74)	65,5(58-72)	0,536
BMI	27,66±2,68	28,1±2,17	0,793
Time LT to COVID-19,days	1164,11±870,91	1147,5±1078,92	0,973
ALT	28(9-112)	68,5(22-110)	0,271
AST	27,5(14-124)	79(34-138)	***0,026***
CRP	80,71±56,42	157,5±68,22	***0,020***
Procalcitonin	0,9(0,07-28,5)	1,5(1,2-2,2)	0,328
Lymphocyte count	1118,84±510,31	575±193,47	***0,047***
D-Dimer	5,5(0,2-3950)	18,15(3,70-2410)	0,391
Ferritin	1352,5(268-6094)	2320(1199-3760)	0,328

5. Discussion

At the onset of pandemia, defining uniform protocols for LT was not possible due to the lack of knowledge of COVID-19. Although there are still no evidence based-guideline, major international hepatology societies have been able to report recommendations to inform LT practices [5, 6, 7]. The main recommendation was limiting LT for the patients with high risk of decompensation and/or HCC. In our country, the first case was seen on March 11, 2020. We followed the recommendations of The Scientific Committee under The Ministry of Health who made the similar suggestions to major international hepatology societies. The reported outcomes of different national and international registries were reviewed in a recent published study [8]. This review indicated that the risk of contracting COVID-19 in LT recipients is similar to that reported in the general population. Fung et al. [9] reported that the clinical presentation in LT recipients were similar to those of immunocompetent patients. We also established the same clinical findings with fever (60%), cough (56.6%) and myalgia (60%) being the three more common symptoms.

Two international registry study reported the outcomes of LT recipients with COVID-19 [10, 11]. The rate of hospitalization was reported as 72% and 82%. On the contrary, the proportion of ICU admission was significantly different in these two studies (10% and 28%). A nationwide cohort study from Spain investigated the 111 LT recipients and the ratio of hospitalization and ICU admission were 86.5% and 10.8%, respectively [12]. Lee et al. [13] reported the single center experience including 38 LT recipients with COVID-19. The rate of hospitalization and ICU admission were 71% and 33% in this study, respectively. Upon the French nationwide registry study, the hospitalization rate was relative low as 64.4% (67/104) and 33% of the patients were taken ICU [14]. In the present study, the rate of ICU admission was 23.3% similar to the reported literature that ranged between %10 and 33%. However, the proportion of the pa-

tients who needed hospitalization was significantly low (36.7%) in our series. Actually, we used the same criteria to define the severity of COVID-19 for hospitalization in the initial diagnosis. But, we also decreased the immunosupresive treatment of the patients who were followed at home and it seems effective to prevent worsening of the COVID-19 in this group.

Despite, no mortality was reported in the limited number of studies [9, 15], the mortality rate was notified between 12% and 20% among LT recipients in the larger studies [10, 14]. In our study, 4 patients who were hospitalized at the initial diagnosis of COVID-19 died (13.3%). The mortality rate among the hospitalized patients and the patients admitted ICU were, 36.3% and 57.1%, respectively. Several studies compared the mortality between LT recipients with COVID-19 and matched general population to investigate the effect of LT on outcome. These studies stated that LT alone did not increase the mortality and LT recipients even had lower or similar mortality [10, 12, 16, 17]. Although most of the studies stated that the presence of comorbidities is significant predictor of adverse outcomes, especially the larger studies reported that comorbidities are not associated with mortality [11-14, 16, 17]. In the present study, our findings related with comorbidities is similar to literature. For that matter, health services accessibility might have an outstanding role on patient outcomes in regard to the presence of comorbidites. The absolute lymphocyte count, AST value and CRP level were predictors factors correlated with mortality in our study. The limited number studies focused on liver injury during COVİD-19 and demonstrated the association between higher levels of hepatocellular enzyme elevation and the severity of COVİD-19 (ICU admission) and even the mortality [8, 14, 17].

The strategy of immunosuppression in LT recipients with COVID-19 varied significantly in the literature. Some studies do not recommend the reduction of immunosuppression regarding with the theory which argues that tissue damage could be due to an immunomediated inflammatory response to the virus[1, 8, 9]. Notwithstanding, a vast number of studies suggested reducing the overall dose of the immunosuppressive therapy, particularly discontinuation of antimetabolites [5, 9-12, 14, 15, 17]. Our immunosupression strategy was also in this direction as mentioned before. This suggestion is originated from the routine managment of the infections in LT recipients. None of our patients experienced graft rejection. However, furher investigations is necessary to determine a firm strategy for immunosupressive therapy in LT recipients with COVID-19.

Unfortunately, the present study has any exact recommendation. Given the lack of conclusive treatment strategy for LT recipients with COVID-19, the purpose of the transplant centers should be overcoming the region spesific challenges for LT in the course of the pandemia.

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