**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 74138

**Manuscript Type:** ORIGINAL ARTICLE

***Case Control Study***

**Impact of COVID-19 pandemic on clinicopathological features of transplant recipients with hepatocellular carcinoma: A case-control study**

Akbulut S *et al*. Effect of COVID-19 on biological behavior HCC

Sami Akbulut, Tevfik Tolga Sahin, Volkan Ince, Sezai Yilmaz

**Sami Akbulut, Tevfik Tolga Sahin, Volkan Ince, Sezai Yilmaz,** Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya 44280, Turkey

**Author contributions:** Akbulut S and Ince Vcollected the data; Akbulut S performed the statistical analysis; Akbulut S and Sahin TT wrote the manuscript; Akbulut S, Sahin TT and Yilmaz S developed the study and reviewed the final version.

**Corresponding author: Sami Akbulut, FACS, MD, PhD, Professor,** Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Elazig Yolu 10.Km, Malatya 44280, Turkey. akbulutsami@gmail.com

**Received:** December 14, 2021

**Revised:** March 17, 2022

**Accepted: April 9, 2022**

**Published online:**

**Abstract**

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic had a significant impact on the management of all diseases. Various diseases such as cancer have a higher risk of COVID-19-related death. Despite this fact, any delay or alteration in treatment of cancer may have fatal consequences. Hepatocellular carcinoma (HCC) is an aggressive liver cancer that requires multimodality treatment to improve survival.

AIM

To evaluate the impact of COVID-19 on the management of patients with HCC by determining changes in demographic, clinical and histopathological variables.

METHODS

Demographic, clinical and pathological variables of patients with HCC who had undergone liver transplantation between March 2020 and June 2021 (Pandemic group, *n* = 48) were retrospectively compared with that of the patients with HCC transplanted between November 2018 and March 2020 (Pre-pandemic group, *n* = 61).

RESULTS

The median age of the patients in the study was 56 (interquartile range = 15). Ninety-seven patients (89%) were male and 12 were female (11%). The most common etiology of liver disease was hepatitis B virus (*n* = 52, 47.7%). According to our results, there was a 21.3% drop in the number of patients transplanted for HCC. There was no difference in the demographic, clinical and pathological characteristics of the patients except blood alkaline phosphatase levels (*P* = 0.029), lymphovascular invasion (*P* = 0.019) and type of the liver graft that was transplanted (*P* = 0.017).

CONCLUSION

It is important to develop a surveillance strategy for liver transplant centers. The liver transplantation for HCC is justified and safe provided that strict surveillance protocols are applied.

**Key Words:** COVID-19 pandemic; Liver transplantation; Hepatocellular carcinoma; Biological behavior

Akbulut S, Sahin TT, Ince V, Yilmaz S. Impact of COVID-19 pandemic on clinicopathological features of transplant recipients with hepatocellular carcinoma: A case-control study. *World J Clin Cases* 2022; In press

**Core Tip:** Thecoronavirus disease 2019 pandemic had a significant impact on the management of all diseases including hepatocellular carcinoma and related chronic liver disease. In this case control study, we aimed to investigate any change in the tumor behavior or change in the management of these patients during the pandemic. This study showed that there was a 21.3% drop in the number of patients transplanted for hepatocellular carcinoma. This study also showed that there were no differences in the demographic, clinical and pathological characteristics of the patients except blood alkaline phosphatase levels, lymphovascular invasion and type of the liver graft that was transplanted.

**INTRODUCTION**

On December 11, 2019, an atypical pneumonia leading to acute respiratory distress syndrome in individuals was reported for the first time in Wuhan city of Hubei Province of China. The etiology was identified to be a new form of coronavirus. Later taxonomic studies defined it to be a new member of the beta-coronavirus family, and was renamed as severe acute respiratory syndrome coronavirus-2. The disease was named as the coronavirus disease 2019 (COVID-19)[1,2]. In Turkey, the first confirmed case of COVID-19 was declared on March 11, 2020. On January 30, 2020, the World Health Organization declared COVID-19 as a public health emergency of international concern, which was a declaration that the situation had become a pandemic and necessary precautions should be taken immediately[3]. COVID-19 soon spread all around the world, and currently there are 255324963 confirmed cases of COVID-19, and 5127696 cumulative deaths are related with COVID-19 and its complications[4]. Since then, there have been 8503220 confirmed cases of COVID-19 in Turkey, and in total 74428 patients died due to COVID-19 and related complications[4].

COVID-19 has overwhelmed the health-care services all around the world. The organization of healthcare facilities was changed, and treatment of many diseases such as heart disease, liver disease and various cancers have been postponed until the pandemic was under control. Also, the COVID-19 pandemic had a significant impact on the emergency procedures. The organization, surveillance strategy and prioritization of the patients should all be reorganized during these periods[5]. Vulnerable populations such as patients with cancer should be determined. As necessary precautions are taken, all nosocomial infections including COVID-19 can be prevented and all emergency procedures can be performed safely[5]. Another point that should be considered is the overwhelming stress and burnout of the health care professionals. As the health care personnel become psychologically burned out, the management of vital diseases such as cancers are disrupted[5,6].

In Turkey, soon after the first confirmed case of COVID-19, the state hospitals were reorganized as the pandemic hospital, and elective surgeries, treatments and daily based procedures such as endoscopies were all cancelled to prevent transmission of COVID-19 between individuals[7]. Liver diseases and transplantation received the hardest blow due to the spread of COVID-19 cases. The use of hospital resources for patients with COVID-19, fear of hospital visits due to risk of disease transmission and economic consequences of the devastating pandemic have crippled the liver transplantation (LT) efforts[8]. In the beginning of the pandemic before the development of vaccination strategies, various societies in the field recommended reduction in the frequency of hospital visits and transplantation procedures in patients with stable disease[9-11]. This strategy has reduced deceased donor liver procurement and transplantation by nearly 80%[12-16]. Soin *et al*[8] reported that living donor LT (LDLT) has dropped by 60% since the beginning of the pandemic in India. Similarly, Bhatti *et al*[17] stated that the LDLTs were on average 70% lower than the pre-COVID-19 period. However, they found that waiting list mortality did not change during the pandemic and pre-pandemic periods, and early mortality rate was found to be even lower than the pre-pandemic period[17].

Hepatocellular carcinoma (HCC) is a very important disease that needs close follow-up for recurrence after treatment or progression following downstaging procedures[18]. However, the risk should be balanced in terms of risk of contracting the disease in a high-risk environment for COVID-19 transmission *vs* the risk of progression or recurrence of HCC in the patients. The patients with HCC have an increased risk of contracting a severe form of COVID-19 for two reasons: (1) They are immunosuppressed because of the cancer treatment; and (2) They are typically of older age and have associated comorbidities that increase the risk of developing severe COVID-19[19,20].

There are many observational studies that have been published in the era of COVID-19 that show that in general cancer patients have a higher mortality risk during COVID-19 infection[21-24]. Specifically, Deng *et al*[21] created a population-based study and showed that the mortality risk increased by 3-fold in cancer patients when they were infected with severe acute respiratory syndrome coronavirus-2. These results have also been confirmed by the study performed by Mehta *et al*[22] stating that the mortality rate of COVID-19 infection among cancer patients were twice the mortality rate in patients without COVID-19.

Furthermore, the care of the patients with HCC has also been interrupted by the overwhelming number of patients with COVID-19[18]. Therefore, patients cannot reach hepatology units for proper care, and diagnostic procedures such as imaging studies, endoscopies and biopsies are delayed. All these factors have detrimental effects on the diagnosis of new HCC tumors and surveillance of the patients that were already receiving medical care[25]. Increased mortality and morbidity in patients with HCC during the pandemic era are due to chronic liver disease. Although chronic liver disease does not specifically increase the susceptibility to COVID-19, specific liver diseases such as fatty liver disease (as a part of the metabolic syndrome) increases the risk of mortality due to severe COVID-19 infection[26,27]. Also, in patients with autoimmune liver disease, immunosuppressive medication used during the treatment of the disease may increase the risk of severe COVID-19 infection[28].

Gandhi *et al*[29] analyzed 27 centers in the Asian-Pacific region where the incidence of HCC was highest. Fourteen of the centers replied to the online questionnaire. Their results showed that there was a nearly 27% drop in the diagnosis of the participating centers; also, there was 50% delay in the diagnosis of HCC. Furthermore, there was a change towards administering oral molecularly targeted systemic therapy in patients with HCC[29]. Similarly, a multicenter study conducted by Muñoz-Martínez *et al*[30] showed dramatic results showing a 40% change in diagnostic procedures, an 87% change in surveillance protocols and a 42% change in the liver transplant program. According to these results, currently more advanced HCC with high drop-out risk were to receive curative treatment such as LT or resection. In our opinion, this would be reflected on the clinicopathologic characteristics of the patients evaluated in transplant centers. However, despite changes in the management and follow-up protocols of patients with HCC, the definitive impact of these changes in patients who received definitive treatment during the pandemic is not clear.

We have also changed our priorities and made changes in the management of patients with end-stage liver disease including HCC. We have previously published our preventive measures and guidelines for handling the infected patients and/or health-care personnel in our institute, which has the highest volume of LDLT in Europe[31]. Therefore, in the present study, our aim was to compare the demographic, clinical and histopathologic characteristics of the patients with HCC during the COVID-19 pandemic with the patients in the pre-pandemic period. We aimed to define any change in the tumor behavior or any change in the management of these patients during the COVID-19 pandemic.

**MATERIALS AND METHODS**

The World Health Organization declared COVID-19 as a public health emergency of international concern on January 30, 2020. The first confirmed case of COVID-19 was declared by the Ministry of Health of Turkey on March 11, 2020. The patients that have been transplanted for HCC in our institute between March 11, 2020 and June 21, 2021 were included in the study. The data of the patients were prospectively collected and retrospectively analyzed. These patients that received operations during the pandemic period were included in the pandemic group. Our aim was to evaluate the impact of COVID-19 on demographic and clinicopathologic characteristics of the patients with HCC; for this reason we included 61 patients who were transplanted for HCC in our institute between November 12, 2018 and March 10, 2020 (before the pandemic) in our study. They were included in the pre-pandemic group. Therefore, we obtained the opportunity to compare the patients with HCC transplanted during the 15 mo peroid after the confirmation of the pandemic in Turkey to the patients with HCC who were transplanted during the 16 mo period before the pandemic. First, the required official administrative permission from the Directorate of the Liver Transplant Institute was granted (Approval date: 04.10.2021 and Number: 93889). Then, ethical approval was obtained from the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval date: 05.10.2021 and Number: 2538).

The study parameters included age (years), sex (female, male), body mass index, graft weight (gram), MELD score, alpha fetoprotein (AFP), tumor number, total diameter of the tumors (TTD; cm), liver index score, Agg index, white blood cell, hemoglobin, platelets, neutrophil, lymphocyte, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, International normalized ratio, creatinine, albumin, total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), lactate dehydrogenase, C-reactive protein, type of LT [LDLT, deceased donor LT (DDLT)], Child score (A, B, C), Milan criteria (single tumor ≤ 5 cm or ≤ 3 tumor with the largest ≤ 3 cm), UCSF criteria (single tumor ≤ 6.5 cm or ≤ 3 tumors with the largest tumor ≤ 4.5 cm and total tumor diameter ≤ 8 cm), BCLC criteria (single tumor ≤ 7 cm, three tumor ≤ 5 cm, five tumor ≤ 3 cm, maintained response within Milan criteria during 6 mo after downstaging), Tokyo 5-5 rule (5 tumor with a maximum tumor size ≤ 5 cm), Onaca criteria (single tumor ≤ 6 cm or 2-4 tumors with the largest tumor ≤ 5 cm), CUN Navara criteria (single tumor ≤ 6 cm or ≤ 3 tumors with the largest ≤ 5 cm), Up-to-7 criteria (total tm diameter ≤ 7 cm and total number of tm ≤ 7), AFP model criteria {[largest tumor size: ≤ 3 cm (0 point), 3–6 cm (1 point), > 6 cm (4 point)] [total number of tumor: 1–3 tumor (0 point), ≥ 4 tumor (2 point) [AFP level: ≤ 100 (0 point), 100–1000 (2 point), > 1000 (3 point)]}, AFP-TTD criteria (AFP ≤ 400 ng/mL and total tumor diameter ≤ 8 cm), expanded Malatya criteria (maximum tumor diameter ≤ 10 cm and AFP ≤ 200 ng/mL and GGT ≤ 104 U/L and within Milan criteria), 5-5-500 rule (nodule size ≤ 5 cm in diameter, nodule number ≤ 5, and AFP ≤ 500 ng/mL), Samsung criteria (≤ 7 tumors, diameter ≤ 6 cm, AFP ≤ 1000 ng/mL), macrovascular invasion (present, absent), tumor differentiation (well, moderate, poor), lymphovascular invasion (present, absent), perineural invasion (present, absent), capsular invasion (present, absent), tumor necrosis (present, absent), locoregional therapy (transarterial radioembolization, transarterial chemoembolization, radiofrequency ablation, microwave ablation, resection, *etc*), ascites (no, moderate, massive), outcome (alive, dead) and recurrence (yes, no).

***Evaluation of patients with HCC who were candidates for LT before the COVID-19 pandemic***

In our institution prior to defining the expanded Malatya criteria[32], patients were considered eligible for LDLT only if the disease was confined to the liver and without any macrovascular invasion. Since 2016, the indication for LT was discussed in multidisciplinary liver tumor board that was constituted by transplant surgeons, medical oncologist, radiologist, nuclear medicine specialist, pathologist and hepatologist. The law commissioned by the Turkish Ministry of Health on organ procurement and allocation allow DDLT in patients with HCC that are within the Milan criteria. However, this does not apply to the recipients of the living liver donors. Therefore, patients with tumors beyond the Milan criteria can only receive LDLT. Our preoperative evaluation includes liver function tests, complete blood counts, coagulation parameters, AFP levels, multi-slice computed tomography scans and magnetic resonance imaging. Recently, we also added positron emission tomography/computerized tomography scan to our work-up scheme.

***Evaluation of patients with HCC that were candidates for LT during the COVID-19 pandemic***

After the confirmation of the first case with COVID-19 in Turkey, the Ministry of Heath released new regulations limiting all elective procedures including elective LTs and advised the liver transplant centers to perform a risk stratification. In addition, emergency LTs, such as those performed for acute liver failure, recipients with a MELD score > 19, patients who were to be transplanted for cancer and patients who were decompensated (intractable ascites, jaundice, encephalopathy and variceal bleeding), during the follow-up period could be performed provided that necessary precautions were taken at the operating room and the patient ward[31]. We have previously published our COVID-19 surveillance strategy in LDLT[31]. In the initial stages of the pandemic, patients with HCC within Milan criteria and with tumors greater than 2 cm were transplanted.

However, various vaccines have been developed, and normalization efforts have started in countries who have vaccinated more than 70% of its population. The organization of the health care centers started to revert to the pre-pandemic state, and elective surgical procedures resumed provided that necessary precautions were taken, as well as COVID-19 surveillance is performed. Therefore, LT for HCC has also returned to its pre-pandemic state. Nevertheless, we are still performing a strict COVID-19 surveillance for our patients and donors (deceased or alive) who will undergo LT.

***Our follow-up protocol after LT***

Our immunosuppressive treatment protocol following LT for HCC is as follows: Corticosteroids are initiated starting from the completion of hepatic artery anastomosis and continues to the postoperative period. The dose is tapered gradually and discontinued on the postoperative third to sixth month. Tacrolimus is initiated on the postoperative third day, and the dose is tapered to obtain trough levels of 6-10 ng/mL. Similarly, mycophenolate mofetil is started on the postoperative third day and is discontinued after the first month in patients who are transplanted for HCC. In the postoperative first month, everolimus is started to achieve trough levels of 8-10 ng/mL, and the tacrolimus dose is tapered to achieve trough levels between 5-7 ng/mL. After the third month following LT, tacrolimus-everolimus combination is continued.

Our postoperative surveillance program is very intense. In the postoperative first 2 years, the AFP levels are analyzed every month. Multi-slice computed tomography is obtained every 3 mo for the first postoperative 2 years. After the second year following the LT, cross-sectional imaging techniques are performed annually. If there is a suspicion of recurrence on laboratory and multi-slice computed tomography, contrast enhanced magnetic resonance imaging and positron emission tomography/computed tomography are performed to confirm the diagnosis. In patients with hepatic recurrence, we perform multimodality treatment including resection, locoregional therapeutic options (transarterial therapies, radiofrequency or microwave ablations) and systemic chemotherapy including sorafenib.

***Statistical analysis***

The statistical analyses were performed using IBM SPSS Statistics v25.0 (Statistical Package for the Social Sciences, Inc, Chicago, IL, United States). The quantitative variables were expressed as median and interquartile range. The qualitative variables were reported as number and percent (%). Kolmogorov–Smirnov were used to assess normality of quantitative variable distribution. Nonparametric Mann Whitney *U* test was used to compare quantitative variables. Pearson’s χ2 test was used to compare qualitative variables. *P* ≤ 0.05 was considered a statistically significant value.

**RESULTS**

***General characteristics of the patients***

In total, 109 patients were included for analysis in the study, and the median age of the patients in the study was 56 (interquartile range = 15). Ninety-seven patients (89%) were male and 12 were female (11%). The common etiologies of liver disease were hepatitis B virus (*n* = 52), cryptogenic (*n* = 26), hepatitis C virus (*n* = 8), hepatitis B virus + hepatitis D virus (*n* = 8) and miscellaneous (*n* = 15). Eight-one patients (74.3%) underwent LT as the primary therapeutic modality, and 28 patients (25.7%) received LT after various modalities of locoregional therapy. One hundred and two patients received LDLT (93.6%), and 7 patients (6.4%) received DDLT. Fifty-nine patients had tumors within the Milan criteria (54.1%), 69 patients (63.3%) were within the UCSF criteria 78 patients (71.6%) were within BCLC criteria, 76 patients were within the 5-5 rule (69.7%), 75 patients (68.8%) were within the Onaca criteria, 69 patients (63.3%) were within the CUN Navara criteria, 75 patients (68.8%) were within the up-to-seven criteria, 74 patients (67.9%) were within AFP model, 78 patients 71.6%) were within AFP-TTD criteria, 73 patients (67%) were within the 5-5-500, 79 patients (72.5%) were within the Samsung criteria, and 75 patients (68.8%) were within the expanded Malatya criteria. Seventeen patients (15.6%) had microvascular invasion, 21 patients (19.3%) had poor differentiation, 46 patients (42.6%) had lymphovascular invasion, 1 patient (0.9%) had perineural invasion, 5 patients (4.6%) showed capsular invasion, and 25 patients (22.9%) had tumor necrosis confirmed by pathologic analysis. The median follow-up period was 571 d (interquartile range = 457; min-max = 17-1051 d). Fifteen patients (13.8%) died during the median follow-up period, and six of the mortalities were within the postoperative first 90 d, which was regarded as early mortality.

***Pre-pandemic vs pandemic era***

Based on March 11, 2020 as the turning point towards the global catastrophe, 61 patients in the pre-pandemic period and 48 patients in the pandemic period underwent LT for HCC. According to our results, there was a 21.3% drop in the number of patients transplanted for HCC. We found no statistical significant difference between groups in terms of age (*P* = 0.685), sex (*P* = 0.629), body mass index (*P* = 0.352), graft weight (*P* = 0.925), MELD score (*n* = 0.413), Child score (*P* = 0.353), pre-LT AFP level (*P* = 0.643), tumor number (*P* = 0256), TTD (*n* = 0.712), liver index score (0.417), Agg index (*P* = 0.183), white blood cell (*P* = 0.298), hemoglobin (*P* = 0.079), platelets (*P* = 0.363), neutrophil (*P* = 0.394), lymphocyte (*P* = 0.498), neutrophil to lymphocyte ratio (*P* = 0.819), platelet to lymphocyte ratio (*P* = 0.634), International normalized ratio (*P* = 0.112), creatinine (*P* = 0.955), albumin (*P* = 0.888), total bilirubin (*P* = 0.138), direct bilirubin (*P* = 0.306), aspartate aminotransferase (*P* = 0.157), alanine aminotransferase (*P* = 0.944), GGT (*P* = 0.213), lactate dehydrogenase (*P* = 0.325), C-reactive protein (*P* = 0.533), Milan criteria (*P* = 0.337), UCSF criteria (*P* = 0.450), BCLC (*P* = 0.429), Tokyo (*P* = 0.684), Onaca (*P* = 0.293), CUN Navara (*P* = 0.450), Up-to-7 (*P* = 0.142), AFP model (*P* = 0.202), AFP-TTD (*P* = 0.223), 5-5-500 rule (*P* = 0.449), Samsung (*P* = 0.229), Malatya (*P* = 0.723) and Extended Malatya (*P* = 0.826).

However, statistically significant differences were found between pre-pandemic and pandemic groups in terms of serum ALP levels (*P* = 0.029), lymphovascular invasion (*P* = 0.019) and type of the liver graft that was transplanted (*P* = 0.017). In patients who were transplanted for HCC in the COVID-19 period, the use of grafts from the living donors was 13.3 times more frequent than the COVID-19 period [odds ratio = 13.3; 95% confidence interval (CI) = 0.74-240]. The rate of lympho-vascular invasion in the explant pathologies of patients was found to be 2.54 times more frequent in patients who received operations during the COVID-19 period (odds ratio = 2.54; 95%CI = 1.15-5.56). Categorical and continuous variables of the groups and results of the statistical analyses are summarized in Tables 1 and 2.

**DISCUSSION**

HCC is the most common primary liver tumor and the fourth to fifth leading cause of cancer-related deaths[33]. HCC usually develops in patients with chronic liver disease and viral hepatitis such as hepatitis B virus and hepatitis C virus play an important etiologic role in its development. The incidence is also rising in developed countries[34]. It meets the criteria of a particular disease that necessitates screening: (1) It is common in individuals of certain subpopulations; (2) Populations at highest risk of developing HCC is defined in detail; (3) Screening tests are non-invasive or minimally invasive; (4) Population at risk usually has underlying chronic liver disease and is subject to regular out-patient follow-up; and (5) Early diagnosis provides advantages in terms of survival and cure of the disease[34,35]. For these reasons, patients with HCC need special attention regarding the course of the disease[35,36]. Any deviation from the standard of care adapted for these patients may have devastating results. In the present study, we evaluated the pre-pandemic and COVID-19 era in terms of clinicopathologic characteristics in patients who were transplanted for HCC. This is one of the first studies evaluating the consequences of the pandemic era on critical diseases such as HCC using the clinicopathologic characteristics.

Various diseases such as cancer need special attention due to their progressive nature, which is especially valid if appropriate treatment is not applied and it may even lead to mortality[37]. On the other hand, the patients with a high risk for mortality due to a severe course of COVID-19 are patients with chronic diseases such as chronic obstructive pulmonary disease, cardiac disease and patients with cancer. In the initial stages of the pandemic, changes were made in the management protocol of every disease including cancer[37,38]. The European Society for Medical Oncology consensus statement stated that treatment of any cancer patients should not be postponed or cancelled without proper risk stratification[39]. HCC is an aggressive tumor with variable tumor biology that has a high tendency to relapse. The recurrence rates following LT and resection are 30% and 70%, respectively[40]. In the initial stages of the pandemic, Gori *et al*[41] published their altered protocol for management of patients with end-stage liver disease including HCC. They prioritized LT for HCC patients with a high risk of progression and drop out. Microwave and radiofrequency ablation were explicitly performed in patients for whom resection was planned; furthermore, locoregional transarterial procedures have been performed as planned but postponed in patients older than 80 years[41]. Iavarone *et al*[38] published the results of this altered protocol in a brief communication. They showed that there was a delay of months or longer in the treatment of 26% of the patients[38]. This delay may have serious consequences for a disease such as HCC.

In the initial stages of the pandemic, we transplanted patients with HCC with tumors greater than 2 cm. However, we developed a strict surveillance program and started to transplant patients according to our conventional protocol. Our results show that using our surveillance protocol there was no difference between the pandemic and pre-pandemic period in terms of the stages of tumors at the time of LT. For this reason, our protocol seems feasible in the management of patients with HCC. However, we found that the rate of lymphovascular invasion was higher in patients transplanted during the COVID-19 period. We believe this may be related to the observational difference between the two time periods because the staging of the tumors (performed by different classification methods) was similar between the two groups, and we have summarized these results in Table 1. Microscopic vascular invasion is an especially major determinant of early recurrence following treatment as well as a major risk factor for metastatic disease[42]. The patients receiving an operation during the pandemic do not have sufficient follow-up period to determine any recurrences. However, similar stages of the disease between the two-time intervals suggests that we may not observe a major difference in the recurrence or the outcome of the patients.

Wu *et al*[43] showed that ALP and GGT were prognostic indictors in patients with HCC undergoing liver resection. Their cohort included 469 pathologically confirmed HCC. They found that high ALP levels (≥ 136.5 IU/mL) were associated with larger tumors (> 5 cm), vascular invasion and advanced BCLC stages[43]. Also, they found that ALP was an independent prognostic factor determining overall survival but not disease-free survival[43]. Both Wu *et al*[43] and other researchers[43-46] have stated that GGT can be a marker for tumor stem cells, microvascular invasion, tumor proliferation and nuclear cell cycle control in the tumors. The results of our study showed that ALP levels were significantly higher in the patients transplanted during the pandemic period. However, there was no significant difference in the GGT levels between the two groups. Therefore, we believe that this is an observational difference and will not have an impact on the survival or recurrence of the patients. However, HCC is a very heterogenous disease in terms of antigenic content, which also reflects upon the biologic behavior. This mosaicism determines the aggressive nature of the tumors[47]. In the present study, only increased microvascular invasion that is a subjective parameter does not determine the absolute outcome of the tumors of the patients. We have also evaluated multiple parameters that show that stages of the tumor did not change when compared to the pre-pandemic period.

During the pandemic, the transplant activities around the world decreased significantly[15,45-48]. Furthermore, the patients with lower scores who were stable were postponed[49-53]. The deceased organ donation significantly decreased even in areas with low COVID-19 incidence[54,55]. Aubert *et al*[56] performed a multi-institutional study and showed that there was a dramatic decrease in both DDLT and LDLT activities[56]. Furthermore, in countries such as Japan where the number of COVID-19 cases as well as COVID-19-related deaths were low and due to strict preventive measures taken, there was a nearly 70% decrease in solid organ transplantation[56]. However, in countries such as the United States, the number of COVID-19 cases as well as the number of deaths were higher, but there was only a 4% decrease in solid organ transplantation[56]. In our institute, the DDLT rates decreased. However, we managed to preserve a relatively high rate of LDLT, which is very unique when considering the study performed by Aubert *et al*[56]. This is the reason we observed a change in the type of the liver graft used in the present study, which was a decrease in the deceased donor organ grafts and an increase in the LDLT in the COVID-19 pandemic. In Turkey, LDLT are generally the mainstay of the liver grafts. Since the relatives are determined to donate their organs for their relatives, the LDLT was sustained in a relatively stable course during the COVID-19 pandemic.

There are various limitations in our study. The major one is the retrospective design of the study. We considered patients who were transplanted for HCC. However, other bridging therapies as well as systemic therapies were not considered. Since our study was not designed as an intention to treat analysis, we cannot draw definitive conclusions regarding the impact of COVID-19 on treatment of patients with HCC. Furthermore, the follow-up period of the patients transplanted during the pandemic is very short. As our survival data accumulates, we can provide better data regarding the significance of increased lymphovascular invasion on the prognosis of the patients. Lastly, the number of patients is low, and results such as increased rate of lymphovascular invasion during the pandemic should be evaluated with a level of skepticism.

**CONCLUSION**

In conclusion, our results show that there was only a modest change in the tumor biology during the COVID-19 pandemic. This shows the efficacy of our surveillance program, which enables transplanting patients with HCC according to conventional management protocols. We believe that the increased lymphovascular invasion rate in the present study is an observational variation because there is no change in the stages of the diseases between the two intervals. The DDLT rate in Turkey is already low, and it further decreased during the pandemic. However, we managed to preserve a high rate of LDLT. Therefore, it is important to develop a surveillance strategy for liver transplant centers. The LT for HCC is justified and safe provided that strict surveillance protocols are applied.

**ARTICLE HIGHLIGHTS**

***Research background***

Coronavirus disease 2019 (COVID-19) has overwhelmed the healthcare services all around the world. The organization of healthcare facilities were changed and treatment of many diseases such as heart disease, liver disease and various cancers have been postponed until the pandemic was under control. Hepatocellular carcinoma (HCC) is an aggressive disease that shows progression without any intervention. Therefore, the impact of COVID-19 in the management of progressive diseases such as HCC needs to be investigated.

***Research motivation***

COVID-19 has overwhelmed the everyday healthcare services. Treatment of many cancers such as liver cancer have been postponed until the COVID-19 pandemic was under control. A delay in the treatment of HCC has serious consequences that would reflect the clinical and tumor characteristics of the patients.

***Research objectives***

The main objective was to compare the demographic, clinical and histopathologic characteristics of the patients with HCC who have undergone liver transplantation during the COVID-19 pandemic with the patients in the pre-pandemic period. We aimed to define any change in the tumor behavior or any change in the management of these patients during the COVID-19 pandemic.

***Research methods***

Demographic, clinicopathological variables of patients with HCC who have undergone liver transplantation between March 2020 and June 2021 (Pandemic group, *n* = 48) were retrospectively compared with that of the patients with HCC transplanted between November 2018 and March 2020 (Pre-pandemic group, *n* = 61).

***Research results***

Ninety-seven patients (89%) were male, and 12 were female (11%). The most common etiology of liver disease was hepatitis B virus (*n* = 52, 47.7%). Statistically significant differences were found between groups in terms of blood alkaline phosphatase levels (*P* = 0.029), lymphovascular invasion (*P* = 0.019) and type of the liver graft that was transplanted (*P* = 0.017). In patients who were transplanted for HCC in the COVID-19 period, the use of grafts from the living donors was 13.3 times more frequent than the pre-COVID-19 period [odds ratio = 13.3; 95% confidence interval (CI): 0.74-240]. The rate of lymphovascular invasion in the explant pathologies of patients was found to be 2.54 times more frequent in patients who received operations during the COVID-19 period (odds ratio = 2.54; 95%CI: 1.15-5.56).

***Research conclusions***

This study showed that there was only a modest change in the tumor biology during the COVID-19 pandemic. This shows the efficacy of our surveillance program that enabled transplanting patients with HCC according to conventional management protocols.

***Research perspectives***

We believe that the increased lymphovascular invasion rate in the present study was an observational variation because there is no change in the stages of the diseases between the two intervals. The DDLT rate in Turkey was already low, and it further decreased during the pandemic. However, we managed to preserve a high rate of LDLT. Therefore, it is important to develop a surveillance strategy for liver transplant centers. The liver transplantation for HCC is justified and safe provided that strict surveillance protocols are applied.

**ACKNOWLEDGEMENTS**

We would like to commend all health care professionals who were always in the frontline. They took the courage and responsibility of treating all patients during these hard times and despite risking their own lives. In addition, we would like to thank Brian I Carr, Ramazan Kutlu, Burak Isik, Nese Karadag, Murat Harputluoglu, Nuru Bayramov, Mustafa Dikilitas, Oztun Temelli, Muge Otlu, Ayse Nur Akatlı, Sinan Karatoprak, and Vedat Subasi, who participated in our online meetings as multidisciplinary liver tumor board member during this process, for their contributions.

**REFERENCES**

1 **Sahin TT**, Akbulut S, Yilmaz S. COVID-19 pandemic: Its impact on liver disease and liver transplantation. *World J Gastroenterol* 2020; **26**: 2987-2999 [PMID: 32587443 DOI: 10.3748/wjg.v26.i22.2987]

2 **Chagas AL**, Fonseca LGD, Coelho FF, Saud LRDC, Abdala E, Andraus W, Fiore L, Moreira AM, Menezes MR, Carnevale FC, Tani CM, Alencar RSSM, D'Albuquerque LAC, Herman P, Carrilho FJ. Management of Hepatocellular Carcinoma during the COVID-19 Pandemic - São Paulo Clínicas Liver Cancer Group Multidisciplinary Consensus Statement. *Clinics (Sao Paulo)* 2020; **75**: e2192 [PMID: 33146360 DOI: 10.6061/clinics/2020/e2192]

3 **WHO**. Official Website of World Health Organization; COVID-19 Dashboard. [cited 10 October 2021]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200130-sitrep-10ncov.pdf?sfvrsn=d0b2e480\_2

4 **WHO**. Coronavirus (COVID-19) Dashboard with Vaccination Data. [cited 10 October 2021]. Available from: https://covid19.who.int

5 **Serban D**, Socea B, Badiu CD, Tudor C, Balasescu SA, Dumitrescu D, Trotea AM, Spataru RI, Vancea G, Dascalu AM, Tanasescu C. Acute surgical abdomen during the COVID-19 pandemic: Clinical and therapeutic challenges. *Exp Ther Med* 2021; **21**: 519 [PMID: 33815592 DOI: 10.3892/etm.2021.9950]

6 **Dimitriu MCT**, Pantea-Stoian A, Smaranda AC, Nica AA, Carap AC, Constantin VD, Davitoiu AM, Cirstoveanu C, Bacalbasa N, Bratu OG, Jacota-Alexe F, Badiu CD, Smarandache CG, Socea B. Burnout syndrome in Romanian medical residents in time of the COVID-19 pandemic. *Med Hypotheses* 2020; **144**: 109972 [PMID: 32531540 DOI: 10.1016/j.mehy.2020.109972]

7 **Turkish Ministry**. Turkish Ministry of Health Scientific Advisory Board Guidelines for the Management of patients with COVID-19 in Hospitals during the pandemic (from website). [cited 10 October 2021]. Available from: https://covid19.saglik.gov.tr/Eklenti/40282/0/covid19saglikkurumlarindacalismarehberiveenfeksiyonkontrolonlemleripdf.pdf

8 **Soin AS**, Choudhary NS, Yadav SK, Saigal S, Saraf N, Rastogi A, Bhangui P, Srinivasan T, Mohan N, Saha SK, Gupta A, Chaudhary RJ, Yadav K, Dhampalwar S, Govil D, Gupta N, Vohra V. Restructuring Living-Donor Liver Transplantation at a High-Volume Center During the COVID-19 Pandemic. *J Clin Exp Hepatol* 2021; **11**: 418-423 [PMID: 33052181 DOI: 10.1016/j.jceh.2020.09.009]

9 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]

10 **Saigal S**, Gupta S, Sudhindran S, Goyal N, Rastogi A, Jacob M, Raja K, Ramamurthy A, Asthana S, Dhiman RK, Singh B, Perumalla R, Malik A, Shanmugham N, Soin AS. Liver transplantation and COVID-19 (Coronavirus) infection: guidelines of the liver transplant Society of India (LTSI). *Hepatol Int* 2020; **14**: 429-431 [PMID: 32270388 DOI: 10.1007/s12072-020-10041-1]

11 **Boettler T**, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Jalan R, Moreau R, Cornberg M, Berg T. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. *JHEP Rep* 2020; **2**: 100169 [PMID: 32835190 DOI: 10.1016/j.jhepr.2020.100169]

12 **Yi SG**, Rogers AW, Saharia A, Aoun M, Faour R, Abdelrahim M, Knight RJ, Grimes K, Bullock S, Hobeika M, McMillan R, Mobley C, Moaddab M, Huang HJ, Bhimaraj A, Ghobrial RM, Gaber AO. Early Experience With COVID-19 and Solid Organ Transplantation at a US High-volume Transplant Center. *Transplantation* 2020; **104**: 2208-2214 [PMID: 32496357 DOI: 10.1097/TP.0000000000003339]

13 **Boyarsky BJ**, Ruck JM, Chiang TP, Werbel WA, Strauss AT, Getsin SN, Jackson KR, Kernodle AB, Van Pilsum Rasmussen SE, Baker TB, Al Ammary F, Durand CM, Avery RK, Massie AB, Segev DL, Garonzik-Wang JM. Evolving Impact of COVID-19 on Transplant Center Practices and Policies in the United States. *Clin Transplant* 2020; **34**: e14086 [PMID: 32918766 DOI: 10.1111/ctr.14086]

14 **El Kassas M**, Alboraie M, Al Balakosy A, Abdeen N, Afify S, Abdalgaber M, Sherief AF, Madkour A, Abdellah Ahmed M, Eltabbakh M, Salaheldin M, Wifi MN. Liver transplantation in the era of COVID-19. *Arab J Gastroenterol* 2020; **21**: 69-75 [PMID: 32439237 DOI: 10.1016/j.ajg.2020.04.019]

15 **Turco C**, Lim C, Soubrane O, Malaquin G, Kerbaul F, Bastien O, Conti F, Scatton O. Impact of the first Covid-19 outbreak on liver transplantation activity in France: A snapshot. *Clin Res Hepatol Gastroenterol* 2021; **45**: 101560 [PMID: 33176991 DOI: 10.1016/j.clinre.2020.10.005]

16 **Gruttadauria S**; Italian Board of Experts in Liver Transplantation (I-BELT) Study Group, The Italian Society of Organ Transplantation (SITO). Preliminary Analysis of the Impact of the Coronavirus Disease 2019 Outbreak on Italian Liver Transplant Programs. *Liver Transpl* 2020; **26**: 941-944 [PMID: 32378325 DOI: 10.1002/lt.25790]

17 **Bhatti ABH**, Nazish M, Khan NY, Manan F, Zia HH, Ilyas A, Ishtiaq W, Khan NA. Living Donor Liver Transplantation During the COVID-19 Pandemic: an Evolving Challenge. *J Gastrointest Surg* 2021; **25**: 3092-3098 [PMID: 34131867 DOI: 10.1007/s11605-021-05057-3]

18 **ILCA Guidance**. ILCA Guidance for Management of HCC during COVID-19 Pandemic. [cited 8 April 2020]. Available from: https://ilca-online.org/awareness/covid-19

19 **Liang W**, Guan W, Chen R, Wang W, Li J, Xu K, Li C, Ai Q, Lu W, Liang H, Li S, He J. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol* 2020; **21**: 335-337 [PMID: 32066541 DOI: 10.1016/S1470-2045(20)30096-6]

20 **Dai M**, Liu D, Liu M, Zhou F, Li G, Chen Z, Zhang Z, You H, Wu M, Zheng Q, Xiong Y, Xiong H, Wang C, Chen C, Xiong F, Zhang Y, Peng Y, Ge S, Zhen B, Yu T, Wang L, Wang H, Liu Y, Chen Y, Mei J, Gao X, Li Z, Gan L, He C, Li Z, Shi Y, Qi Y, Yang J, Tenen DG, Chai L, Mucci LA, Santillana M, Cai H. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. *Cancer Discov* 2020; **10**: 783-791 [PMID: 32345594 DOI: 10.1158/2159-8290.CD-20-0422]

21 **Deng G**, Yin M, Chen X, Zeng F. Clinical determinants for fatality of 44,672 patients with COVID-19. *Crit Care* 2020; **24**: 179 [PMID: 32345311 DOI: 10.1186/s13054-020-02902-w]

22 **Mehta V**, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, Pradhan K, Thota R, Reissman S, Sparano JA, Gartrell BA, Smith RV, Ohri N, Garg M, Racine AD, Kalnicki S, Perez-Soler R, Halmos B, Verma A. Case Fatality Rate of Cancer Patients with COVID-19 in a New York Hospital System. *Cancer Discov* 2020; **10**: 935-941 [PMID: 32357994 DOI: 10.1158/2159-8290.CD-20-0516]

23 **Zhang L**, Zhu F, Xie L, Wang C, Wang J, Chen R, Jia P, Guan HQ, Peng L, Chen Y, Peng P, Zhang P, Chu Q, Shen Q, Wang Y, Xu SY, Zhao JP, Zhou M. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol* 2020; **31**: 894-901 [PMID: 32224151 DOI: 10.1016/j.annonc.2020.03.296]

24 **Kuderer NM**, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, Shete S, Hsu CY, Desai A, de Lima Lopes G Jr, Grivas P, Painter CA, Peters S, Thompson MA, Bakouny Z, Batist G, Bekaii-Saab T, Bilen MA, Bouganim N, Larroya MB, Castellano D, Del Prete SA, Doroshow DB, Egan PC, Elkrief A, Farmakiotis D, Flora D, Galsky MD, Glover MJ, Griffiths EA, Gulati AP, Gupta S, Hafez N, Halfdanarson TR, Hawley JE, Hsu E, Kasi A, Khaki AR, Lemmon CA, Lewis C, Logan B, Masters T, McKay RR, Mesa RA, Morgans AK, Mulcahy MF, Panagiotou OA, Peddi P, Pennell NA, Reynolds K, Rosen LR, Rosovsky R, Salazar M, Schmidt A, Shah SA, Shaya JA, Steinharter J, Stockerl-Goldstein KE, Subbiah S, Vinh DC, Wehbe FH, Weissmann LB, Wu JT, Wulff-Burchfield E, Xie Z, Yeh A, Yu PP, Zhou AY, Zubiri L, Mishra S, Lyman GH, Rini BI, Warner JL; COVID-19 and Cancer Consortium. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet* 2020; **395**: 1907-1918 [PMID: 32473681 DOI: 10.1016/S0140-6736(20)31187-9]

25 **Boettler T**, Newsome PN, Mondelli MU, Maticic M, Cordero E, Cornberg M, Berg T. Care of patients with liver disease during the COVID-19 pandemic: EASL-ESCMID position paper. *JHEP Rep* 2020; **2**: 100113 [PMID: 32289115 DOI: 10.1016/j.jhepr.2020.100113]

26 **Cai Q**, Chen F, Wang T, Luo F, Liu X, Wu Q, He Q, Wang Z, Liu Y, Liu L, Chen J, Xu L. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China. *Diabetes Care* 2020; **43**: 1392-1398 [PMID: 32409502 DOI: 10.2337/dc20-0576]

27 **Docherty AB**, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369**: m1985 [PMID: 32444460 DOI: 10.1136/bmj.m1985]

28 **Brenner EJ**, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Ruemmele FM, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology* 2020; **159**: 481-491.e3 [PMID: 32425234 DOI: 10.1053/j.gastro.2020.05.032]

29 **Gandhi M**, Ling WH, Chen CH, Lee JH, Kudo M, Chanwat R, Strasser SI, Xu Z, Lai SH, Chow PK. Impact of COVID-19 on Hepatocellular Carcinoma Management: A Multicountry and Region Study. *J Hepatocell Carcinoma* 2021; **8**: 1159-1167 [PMID: 34589445 DOI: 10.2147/JHC.S329018]

30 **Muñoz-Martínez S**, Sapena V, Forner A, Nault JC, Sapisochin G, Rimassa L, Sangro B, Bruix J, Sanduzzi-Zamparelli M, Hołówko W, El Kassas M, Mocan T, Bouattour M, Merle P, Hoogwater FJH, Alqahtani SA, Reeves HL, Pinato DJ, Giorgakis E, Meyer T, Villadsen GE, Wege H, Salati M, Mínguez B, Di Costanzo GG, Roderburg C, Tacke F, Varela M, Galle PR, Alvares-da-Silva MR, Trojan J, Bridgewater J, Cabibbo G, Toso C, Lachenmayer A, Casadei-Gardini A, Toyoda H, Lüdde T, Villani R, Matilla Peña AM, Guedes Leal CR, Ronzoni M, Delgado M, Perelló C, Pascual S, Lledó JL, Argemi J, Basu B, da Fonseca L, Acevedo J, Siebenhüner AR, Braconi C, Meyers BM, Granito A, Sala M, Rodríguez-Lope C, Blaise L, Romero-Gómez M, Piñero F, Gomez D, Mello V, Pinheiro Alves RC, França A, Branco F, Brandi G, Pereira G, Coll S, Guarino M, Benítez C, Anders MM, Bandi JC, Vergara M, Calvo M, Peck-Radosavljevic M, García-Juárez I, Cardinale V, Lozano M, Gambato M, Okolicsanyi S, Morales-Arraez D, Elvevi A, Muñoz AE, Lué A, Iavarone M, Reig M. Assessing the impact of COVID-19 on liver cancer management (CERO-19). *JHEP Rep* 2021; **3**: 100260 [PMID: 33644725 DOI: 10.1016/j.jhepr.2021.100260]

31 **Baskiran A**, Akbulut S, Sahin TT, Tuncer A, Kaplan K, Bayindir Y, Yilmaz S. Coronavirus Precautions: Experience of High Volume Liver Transplant Institute. *Turk J Gastroenterol* 2022; **33**: 145-152 [PMID: 35115295 DOI: 10.5152/tjg.2022.21748]

32 **Ince V**, Carr BI, Bag HG, Ersan V, Usta S, Koc C, Gonultas F, Sarici BK, Karakas S, Kutluturk K, Baskiran A, Yilmaz S. Liver transplant for large hepatocellular carcinoma in Malatya: The role of gamma glutamyl transferase and alpha-fetoprotein, a retrospective cohort study. *World J Gastrointest Surg* 2020; **12:** 520-533 [PMID: 33437403 DOI: 10.4240/wjgs.v12.i12.520]

33 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

34 **El-Serag HB**, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. *Ann Intern Med* 2003; **139**: 817-823 [PMID: 14623619 DOI: 10.7326/0003-4819-139-10-200311180-00009]

35 **Prorok PC**. Epidemiologic approach for cancer screening. Problems in design and analysis of trials. *Am J Pediatr Hematol Oncol* 1992; **14**: 117-128 [PMID: 1530116 DOI: 10.1097/00043426-199205000-00005]

36 **Ayuso C**, Rimola J, Vilana R, Burrel M, Darnell A, García-Criado Á, Bianchi L, Belmonte E, Caparroz C, Barrufet M, Bruix J, Brú C. Diagnosis and staging of hepatocellular carcinoma (HCC): current guidelines. *Eur J Radiol* 2018; **101**: 72-81 [PMID: 29571804 DOI: 10.1016/j.ejrad.2018.01.025]

37 **Curigliano G**, Banerjee S, Cervantes A, Garassino MC, Garrido P, Girard N, Haanen J, Jordan K, Lordick F, Machiels JP, Michielin O, Peters S, Tabernero J, Douillard JY, Pentheroudakis G; Panel members. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. *Ann Oncol* 2020; **31**: 1320-1335 [PMID: 32745693 DOI: 10.1016/j.annonc.2020.07.010]

38 **Iavarone M**, Sangiovanni A, Carrafiello G, Rossi G, Lampertico P. Management of hepatocellular carcinoma in the time of COVID-19. *Ann Oncol* 2020; **31**: 1084-1085 [PMID: 32330540 DOI: 10.1016/j.annonc.2020.04.007]

39 **ESMO**. ESMO’S expert consensus: do not discontinue or delay cancer treatment that may impact on overall survival. [cited 8 April 2020]. Available from: https://www.esmo.org/newsroom/press-office

40 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P; Metroticket Investigator Study Group. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]

41 **Gori A**, Dondossola D, Antonelli B, Mangioni D, Alagna L, Reggiani P, Bandera A, Rossi G. Coronavirus disease 2019 and transplantation: A view from the inside. *Am J Transplant* 2020; **20**: 1939-1940 [PMID: 32181969 DOI: 10.1111/ajt.15853]

42 **Wang W**, Guo Y, Zhong J, Wang Q, Wang X, Wei H, Li J, Xiu P. The clinical significance of microvascular invasion in the surgical planning and postoperative sequential treatment in hepatocellular carcinoma. *Sci Rep* 2021; **11**: 2415 [PMID: 33510294 DOI: 10.1038/s41598-021-82058-x]

43 **Wu SJ**, Lin YX, Ye H, Xiong XZ, Li FY, Cheng NS. Prognostic value of alkaline phosphatase, gamma-glutamyl transpeptidase and lactate dehydrogenase in hepatocellular carcinoma patients treated with liver resection. *Int J Surg* 2016; **36**: 143-151 [PMID: 27793641 DOI: 10.1016/j.ijsu.2016.10.033]

44 **Xu XS**, Wan Y, Song SD, Chen W, Miao RC, Zhou YY, Zhang LQ, Qu K, Liu SN, Zhang YL, Dong YF, Liu C. Model based on γ-glutamyltransferase and alkaline phosphatase for hepatocellular carcinoma prognosis. *World J Gastroenterol* 2014; **20**: 10944-10952 [PMID: 25152598 DOI: 10.3748/wjg.v20.i31.10944]

45 **Yu MC**, Chan KM, Lee CF, Lee YS, Eldeen FZ, Chou HS, Lee WC, Chen MF. Alkaline phosphatase: does it have a role in predicting hepatocellular carcinoma recurrence? *J Gastrointest Surg* 2011; **15**: 1440-1449 [PMID: 21541770 DOI: 10.1007/s11605-011-1537-3]

46 **Yamamoto K**, Awogi T, Okuyama K, Takahashi N. Nuclear localization of alkaline phosphatase in cultured human cancer cells. *Med Electron Microsc* 2003; **36**: 47-51 [PMID: 12658351 DOI: 10.1007/s007950300006]

47 **Ceausu M**, Socea B, Serban D, Smarandache CG, Predescu D, Bacalbaşa N, Slavu I, Tulin A, Alecu L, Ceauşu Z. Heterogeneity of antigenic constellation in human hepatocellular carcinoma. *Exp Ther Med* 2021; **21**: 270 [PMID: 33603877 DOI: 10.3892/etm.2021.9701]

48 **Georgiades F**, Summers DM, Butler AJ, Russell NKI, Clatworthy MR, Torpey N. Renal transplantation during the SARS-CoV-2 pandemic in the UK: Experience from a large-volume center. *Clin Transplant* 2021; **35**: e14150 [PMID: 33170982 DOI: 10.1111/ctr.14150]

49 **Domínguez-Gil B**, Fernández-Ruiz M, Hernández D, Crespo M, Colmenero J, Coll E, Rubio JJ. Organ Donation and Transplantation During the COVID-19 Pandemic: A Summary of the Spanish Experience. *Transplantation* 2021; **105**: 29-36 [PMID: 33165237 DOI: 10.1097/TP.0000000000003528]

50 **Hallett A**, Motter JD, Frey A, Higgins RS, Bush EL, Snyder J, Garonzik-Wang JM, Segev DL, Massie AB. Trends in Heart and Lung Transplantation in the United States Across the COVID-19 Pandemic. *Transplant Direct* 2021; **7**: e759 [PMID: 34514114 DOI: 10.1097/TXD.0000000000001224]

51 **Zaidan M**, Legendre C. Solid Organ Transplantation in the Era of COVID-19: Lessons from France. *Transplantation* 2021; **105**: 61-66 [PMID: 33208691 DOI: 10.1097/TP.0000000000003536]

52 **Bellini MI**, Tortorici F, Capogni M. COVID-19 in solid organ transplantation: an analysis of the impact on transplant activity and wait lists. *Transpl Int* 2021; **34**: 209-212 [PMID: 33111334 DOI: 10.1111/tri.13779]

53 **Strauss AT**, Boyarsky BJ, Garonzik-Wang JM, Werbel W, Durand CM, Avery RK, Jackson KR, Kernodle AB, Baker T, Snyder J, Segev DL, Massie AB. Liver transplantation in the United States during the COVID-19 pandemic: National and center-level responses. *Am J Transplant* 2021; **21**: 1838-1847 [PMID: 33107180 DOI: 10.1111/ajt.16373]

54 **Coll E**, Fernández-Ruiz M, Sánchez-Álvarez JE, Martínez-Fernández JR, Crespo M, Gayoso J, Bada-Bosch T, Oppenheimer F, Moreso F, López-Oliva MO, Melilli E, Rodríguez-Ferrero ML, Bravo C, Burgos E, Facundo C, Lorenzo I, Yañez Í, Galeano C, Roca A, Cabello M, Gómez-Bueno M, García-Cosío M, Graus J, Lladó L, de Pablo A, Loinaz C, Aguado B, Hernández D, Domínguez-Gil B; Spanish Group for the Study of COVID-19 in Transplant Recipients. COVID-19 in transplant recipients: The Spanish experience. *Am J Transplant* 2021; **21**: 1825-1837 [PMID: 33098200 DOI: 10.1111/ajt.16369]

55 **Chadban SJ**, McDonald M, Wyburn K, Opdam H, Barry L, Coates PT. Significant impact of COVID-19 on organ donation and transplantation in a low-prevalence country: Australia. *Kidney Int* 2020; **98**: 1616-1618 [PMID: 33096085 DOI: 10.1016/j.kint.2020.10.007]

56 **Aubert O**, Yoo D, Zielinski D, Cozzi E, Cardillo M, Dürr M, Domínguez-Gil B, Coll E, Da Silva MI, Sallinen V, Lemström K, Midtvedt K, Ulloa C, Immer F, Weissenbacher A, Vallant N, Basic-Jukic N, Tanabe K, Papatheodoridis G, Menoudakou G, Torres M, Soratti C, Hansen Krogh D, Lefaucheur C, Ferreira G, Silva HT Jr, Hartell D, Forsythe J, Mumford L, Reese PP, Kerbaul F, Jacquelinet C, Vogelaar S, Papalois V, Loupy A. COVID-19 pandemic and worldwide organ transplantation: a population-based study. *Lancet Public Health* 2021; **6**: e709-e719 [PMID: 34474014 DOI: 10.1016/S2468-2667(21)00200-0]

**Footnotes**

**Institutional review board statement:** This study was reviewed and approved by the Inonu University institutional review board for non-interventional studies, No. 2021/2538.

**Informed consent statement:** Verbal and written consents were obtained from all HCC patients before the liver transplantation procedure.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest regarding this study.

**Data sharing statement:** There are no additional data available for this study.

**STROBE statement:** The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** December 14, 2021

**First decision:** March 12, 2022

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Turkey

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ling Q, China; Socea B, Romania **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:** Fan JR

**Table 1** **Comparison of pre-pandemic and pandemic groups in terms of categorical variables**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Pre-pandemic, *n* = 61** | **Pandemic, *n* = 48** | **Total, *n* = 109** | ***P* value** |
| **Sex (%)** |  |  |  | 0.629 |
| Male | 53 (86.9) | 44 (91.7) | 97 (89) |
| Female | 8 (13.1) | 4 (8.3 | 12 (11) |
| **LT type** |  |  |  | 0.017 |
| LDLT | 54 (88.5) | 48 (100) | 102 (93.6) |
| DDLT | 7 (11.5) | 0 (0) | 7 (6.4) |
| **Child score** |  |  |  | 0.353 |
| A | 22 (36.1) | 12 (25.0) | 34 (31.2) |
| B | 27 (44.3) | 22 (45.8) | 49 (45.0) |
| C  | 12 (19.7) | 14 (29.2) | 26 (23.8) |
| **Milan criteria** |  |  |  | 0.337 |
| Within | 36 (59.0) | 23 (47.9) | 59 (54.1) |
| Beyond | 25 (41.0) | 25 (52.1) | 50 (45.9) |
| **UCSF criteria** |  |  |  | 0.450 |
| Within | 41 (67.2) | 28 (58.3 | 69 (63.3) |
| Beyond | 20 (32.8) | 20 (41.7) | 40 (36.7) |
| **BCLC criteria** |  |  |  | 0.429 |
| Within | 46 (75.4) | 32 (66.7) | 78 (71.6) |
| Beyond | 15 (24.6) | 16 (33.3) | 31 (28.4) |
| **Tokyo (5-5 rule)** |  |  |  | 0.684 |
| Within | 44 (72.1) | 32 (66.7) | 76 (69.7) |
| Beyond | 17 (27.9) | 16 (33.3) | 33 (30.3) |
| **Onaca criteria** |  |  |  | 0.293 |
| Within | 45 (73.8) | 30 (62.5) | 75 (68.8) |
| Beyond | 16 (26.2) | 18 (37.5) | 34 (31.2) |
| **CUN navara criteria** |  |  |  | 0.450 |
| Within | 41 (67.2) | 28 (58.3) | 69 (63.3) |
| Beyond | 20 (32.8) | 20 (41.7) | 40 (36.7) |
| **Up-to-7 criteria** |  |  |  | 0.142 |
| Within | 46 (75.4) | 29 (60.4) | 75 (68.8) |
| Beyond | 15 (24.6) | 19 (39.4 | 34 (31.2) |
| **AFP model** |  |  |  | 0.202 |
| Within | 45 (73.8) | 29 (60.4) | 74 (67.9) |
| Beyond | 16 (26.2) | 19 (39.6) | 35 (32.1) |
| **AFP-TTD criteria** |  |  |  | 0.223 |
| Within | 47 (77.0) | 31 (64.6) | 78 (71.6) |
| Beyond | 14 (23.0) | 17 (35.4) | 31 (28.4) |
| **Expanded Malatya criteria** |  |  |  | 0.826 |
| Within | 43 (70.5) | 32 (66.7) | 75 (68.8) |
| Beyond | 18 (29.5) | 16 (33.3) | 34 (31.2) |
| **5-5-500 rule** |  |  |  | 0.449 |
| Within | 43 (70.5) | 30 (62.5) | 73 (67.0) |  |
| Beyond | 18 (29.5) | 18 (37.5) | 36 (33.0) |  |
| **Samsung criteria** |  |  |  | 0.229 |
| Within | 47 (77.0) | 32 (66.7) | 79 (72.5) |  |
| Beyond | 14 (23.0) | 16 (33.3 | 30 (27.5) |  |
| **Macrovascular invasion** |  |  |  | 0.284 |
| Present | 7 (11.5) | 10 (20.8) | 17 (15.6) |  |
| Absent | 54 (88.5) | 38 (79.2) | 92 (84.4) |  |
| **Tumor differentiation** |  |  |  | 0.066 |
| Well | 31 (50.8) | 20 (41.7) | 51 (46.8) |  |
| Moderate | 23 (37.7) | 14 (29.2) | 37 (33.9) |  |
| Poor | 7 (11.5) | 14 (29.2) | 21 (19.3) |  |
| **Lympho-vascular invasion** |  |  |  | 0.019 |
| Present | 20 (32.8) | 26 (55.3) | 46 (42.6) |  |
| Absent | 41 (67.2) | 21 (44.7) | 62 (57.4) |  |
| **Perineural invasion** |  |  |  | 0.435 |
| Present | 0 (0.0) | 1 (2.1) | 1 (0.9) |  |
| Absent | 61 (100) | 46 (97.9) | 108 (98.2) |  |
| **Capsular inasion** |  |  |  | 0.651 |
| Present | 2 (3.3) | 3 (6.4) | 5 (4.6) |  |
| Absent | 59 (96.7) | 44 (93.6) | 103 (94.5) |  |
| **Tumor necrosis** |  |  |  | 0.526 |
| Present | 16 (26.2) | 9 (19.1) | 25 (22.9) |  |
| Absent | 45 (73.8) | 38 (80.9) | 83 (76.1) |  |
| **Locoregional therapy ascites** |  |  |  | 1.000 |
| Yes | 16 (26.2) | 12 (25.0) | 28 (25.7) |  |
| No | 45 (73.8) | 36 (75.0) | 81 (74.3) |  |
| **Ascites** |  |  |  | 0.113 |
| Mild | 32 (52.5) | 25 (52.1) | 57 (52.3) |  |
| Moderate | 22 (36.1) | 11 (22.9) | 33 (30.3) |  |
| Massive | 7 (11.5) | 12 (25.0) | 19 (17.4) |  |
| **Outcome** |  |  |  | 0.953 |
| Alive | 52 (85.2) | 42 (87.5) | 94 (86.2) |  |
| Dead | 9 (14.8) | 6 (12.5) | 15 (13.8) |  |
| **Recurrence** |  |  |  | 0.693 |
| Yes | 4 (6.6) | 2 (4.2) | 6 (5.5) |  |
| No | 57 (93.4) | 46 (95.8) | 103 (64.5) |  |

AFP: Alpha fetoprotein; LT: Liver transplantation; LDLT: Living donor liver transplantation; DDLT: Deceased donor liver transplantation; TTD: Total diameter of the tumors.

**Table 2 Comparison of pre-pandemic and pandemic groups in terms of continuous variables**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **Pre-pandemic**  | **Pandemic** | ***P* value** |
| **Median (IQR)** | **95%CI** | **Median (IQR)** | **95%CI** |
| Age  | 56 (17) | 52-59 | 56 (14) | 53-59 | 0.685 |
| BMI  | 26 (5) | 24-27 | 27 (5) | 25-28 | 0.352 |
| Graft weight | 810 (220) | 760-825 | 827 (272) | 735-920 | 0.925 |
| MELD score | 15 (10) | 12-17 | 16 (8) | 13-18 | 0.413 |
| AFP level | 9 (36) | 5-13 | 11 (82) | 6-25 | 0.643 |
| Tumor number | 1 (3) | 1-2 | 2 (2) | 1-3 | 0.256 |
| TTD | 3.3 (3.8) | 2.5-4.5 | 3.7 (6.3) | 2.0-6.0 | 0.712 |
| Liver index score | 7 (2) | 7-7 | 7 (2) | 7-8 | 0.417 |
| Agg index | 4.0 (2.0) | 4.0-5.0 | 5.0 (2.5) | 4.0-6.0 | 0.183 |
| WBC | 6.0 (2.8) | 5.0-7.0 | 4.9 (3.2) | 4.0-6.0 | 0.298 |
| Hb | 13.0 (3.7) | 12.0-14.0 | 11.9 (3.5) | 11.0-13.0 | 0.079 |
| Platelets | 95 (90) | 77-113 | 83 (102) | 58-128 | 0.363 |
| Neutrophil | 3.5 (2.7) | 2.9-4.1 | 2.8 (2.2) | 2.5-3.7 | 0.394 |
| Lymphocyte | 1.1 (0.9) | 0.9-1.6 | 1.1 (0.9) | 0.9-1.3 | 0.498 |
| NLR | 2.7 (2.9) | 2.1-3.4 | 2.6 (1.9) | 2.1-3.1 | 0.819 |
| PLR | 76 (50) | 64-91 | 76 (61) | 59-93 | 0.634 |
| INR | 1.26 (0.40) | 1.22-1.37 | 1.33 (0.43) | 1.28-1.46 | 0.112 |
| Creatinine | 0.8 (0.3) | 0.7-0.9 | 0.8 (0.2) | 0.7-0.9 | 0.955 |
| Albumin | 2.9 (1.2) | 2.6-3.1 | 2.9 (1.1) | 2.6-3.1 | 0.888 |
| Total bilirubin | 1.7 (2.3) | 1.2-2.1 | 2.3 (4.0) | 1.4-2.8 | 0.138 |
| Direct bilirubin  | 0.8 (1.4) | 0.6-1.0 | 1.1 (1.5) | 0.7-1.3 | 0.306 |
| AST  | 57 (47) | 46-63 | 57 (67) | 46-86 | 0.157 |
| ALT | 41 (38) | 33-50 | 40 (32) | 30-52 | 0.944 |
| ALP | 107 (74) | 93-122 | 131 (123) | 109-158 | 0.029 |
| GGT | 78 (83) | 61-107 | 61 (78) | 44-105 | 0.213 |
| LDH | 224 (91) | 202-255 | 247 (99) | 210-273 | 0.325 |
| CRP | 0.7 (1.4) | 0.4-1.2 | 0.9 (1.8) | 0.5-1.9 | 0.533 |

95% confidence interval (CI) for median values. BMI: Body mass index; AFP: Alpha fetoprotein; WBC: White blood cell; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; INR: International normalized ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Glutamyl transpeptidase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; TTD: Total diameter of the tumors; Hb: Hemoglobin; IQR: Interquartile range.