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Case Control Study

Effect of the COVID-19 Pandemic on Clinicopathological Features of HCC Patients Who Have Undergone Liver Transplantation: Case-Control Study

Effect of Covid-19 on biological behavior HCC

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Abstract

BACKGROUND

COVID-19 pandemic had significant impact on the management of all diseases. Various disease such as cancer has 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 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).

RESULTS

The median age of the patients in the study was 56 (IQR=15). Ninety-seven patients (89%) were male and12 were female (11%). The most common etiology of liver disease was HBV (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 ALP levels (P = 0.029), lympho-vascular invasion (P = 0.019) and type of the liver graft that is 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; SARS-CoV-2 outbreak; Liver transplantation; Hepatocellular carcinoma; Biological behavior

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Core Tip: COVID-19 pandemic had significant impact on the management of all diseases including hepatocellular carcinoma and related chronic liver disease. In this case control study, we aim to investigate any change in the tumor behavior or any change in the management of these patients during the COVID-19 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 was no difference in the demographic , clinical and pathological characteristics of the patients except blood ALP levels, lympho-vascular invasion and type of the liver graft that is transplanted.

INTRODUCTION

In December 11th, 2019 an atypical pneumonia leading to acute respiratory distress syndrome in individuals were reported for the first time in Wuhan city of Hubei Province of China. The etiology was identified to be a new form of coronavirus (nCOV) and later taxonomic studies defined it to be new member of the beta-coronavirus family and wad re-named as Severe Acute Respiratory Distress Syndrome-Corona Virus-2 (SARS-CoV-2) and the disease was named as the corona virus infectious disease-2019 (COVID-19) [1,2]. In Turkey, the first confirmed case of COVID-19 was declared in March 11th, 2020. In January 30th, 2020 World Health Organization (WHO) declared COVID-

19 as a public health emergency of international concern (PHEIC) 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 255,324,963 confirmed cases of COVID-19 and 5,127,696 cumulative deaths are related with COVID-19 and its complications [4]. Since then, there have been 8,503,220 confirmed cases of COVID-19 in Turkey and in total 74,428 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 the 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. Also, COVID-19 pandemic had 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. Because as the health care personnel becomes psychologically burned our 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 re-organized 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 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 efforts [8]. In the beginning of the pandemic before the development of vaccination strategies, various societies in the field have recommended to reduce 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] have reported that LDLT has dropped by 60% in the beginning of the pandemic in India. Similarly, Bhatti *et al* [17] have 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 pandemic and pre-pandemic periods and early mortality rate was found to be event 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 down-staging 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 increased risk of contracting severe form of COVID-19 for two reasons; first one is the fact that these patients are cancer patients. They are immunosuppressed because of the cancer treatment. In addition, they have older age and associated co-morbidities 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 higher mortality risk during the COVID-19 infection [21-24]. Specifically, Deng and colleagues [21] have made a population-based study and have shown that the mortality risk increased by 3-folds in cancer patients when they are infected with SARS-CoV-2. These results have also been confirmed by the study performed by Mehta and colleagues [22] stating that the mortality rate of COVID-19 infection among cancer patents 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 patents with COVID-19 [18]. Therefore, patients cannot reach hepatology units for proper care and even if they due 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 also surveillance of the patients that were already receiving medical care [25]. The second reason for increased mortality and morbidity in patents with HCC during the pandemic era is due to the fact that these patients have

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 and colleagues [29] have analyzed 27 centers in the Asian-Pacific region where incidence of HCC was highest. Fourteen of the centers replied to the on-line questionnaire. Their results showed that there was 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, multicenter study conducted by Munoz-Martinez and colleagues [30] have shown dramatic results showing 40% change in diagnostic procedures, 87% change in surveillance protocols, 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 liver transplantation or resection. In our opinion, this would be reflected on the clinico-pathologic characteristics of the patients evaluated in transplant centers. However, despite changes in the management and follow-up protocols the 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 patents and/or health-care personnel in our institute which is has the highest volume of LDLT in Europe [31]. Therefore, in the present study, our aim is to compare the demographic, clinical and histopathologic characteristics of the patients with HCC in the COVID-19 pandemic with the patients in the pre-pandemic period. We aim 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

+ADw-html+AD4APA-p+AD4-WHO declared COVID-19 as public health-emergency of international concern (PHEIC) in 30 January 2020. The first confirmed case of COVID-19 was declared by the Ministry of Health of Turkey on March 11th, 2020. The patients that have been transplanted for HCC in our institute between March 11th, 2020 and June 21st, 2021 included in the study. The Data of the patients were prospectively collected and retrospectively analyzed. These patients that were operated during the pandemic period were included in the study group. Our aim was to evaluate the impact of COVID-19 on demographic and clinicopathologic characteristics of the patients with HCC+ADs- and for this reason we included 61 patients who were transplanted for HCC in our institute between November 12th 2018 and March 10th 2020 (before the pandemic) in our study and they were included in the pre-pandemic group. Therefore, we obtained the opportunity to compare the patients with HCC transplanted for 15 mo after the confirmation of the pandemic in Turkey to the patients with HCC who were transplanted during the pre-pandemic 16 mo. This retrospective study was approved by the Inonu University institutional review board for non-interventional studies (Approval No: 2021/2538).+ADw-br /+AD4-The study parameters included age (years), sex (female, male), body mass index (BMI), graft weight (gram), MELD score, alpha fetoprotein (AFP), tumor number, +ACY-nbsp+ADs-total diameter of the tumors (TTD+ADs- cm), Liver index score, Agg index, white blood cell (WBC), hemoglobin (Hb), platelets, neutrophil, lymphocyte, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), International normalized ratio (INR), creatinine, albumin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), +ACY-nbsp+ADs-lactate dehydrogenase (LDH), +ACY-nbsp+ADs-C-reactive protein (CRP), type of LT (living donor liver transplantation +AFs-LDLT+AF0-, deceased donor liver transplantation +AFs-DDLT+AF0-), Child score (A, B, C), Milan criteria (single tumor +ACY-le+ADs- 5 cm or +ACY-le+ADs- 3 tumor with the largest

+ACY-le+ADs- 3 cm), UCSF criteria (single tumor +ACY-le+ADs- 6.5 cm or +ACY-le+ADs- 3 tumors with the largest tumor +ACY-le+ADs- 4.5 cm and total tumor diameter +ACY-le+ADs- 8 cm), BCLC criteria (single tumor +ACY-le+ADs- 7 cm, three tumor +ACY-le+ADs- 5 cm, five tumor +ACY-le+ADs- 3 cm, maintained response within Milan criteria during 6 mo after downstaging), Tokyo 5-5 rule (5 tumor with a maximum tumor size +ACY-nbsp+ADsAJg-le+ADs- 5 cm), Onaca criteria (single tumor +ACY-le+ADs- 6 cm or 2-4 tumors with the largest tumor +ACY-le+ADs- 5 cm), CUN Navara criteria (single tumor +ACY-le+ADs- 6 cm or +ACY-le+ADs- 3 tumors with the largest +ACY-le+ADs- 5 cm), Up-to-7 criteria (total tm diameter +ACY-le+ADs- 7 cm and total number of tm +ACY-le+ADs- 7), AFP model criteria (+AFs-largest tumor size: +ACY-nbsp+ADsAJg-le+ADs- 3 cm +AHs-0 point+AH0-, 3+ACY-ndash+ADs-6 cm +AHs-1 point+AH0-, +ACY-gt+ADs- 6 cm +AHs-4 point+AH0AXQ- +AFs-total number of tumor: 1+ACY-ndash+ADs-3 tumor +AHs-0 point+AH0-, +ACY-ge+ADs- 4 tumor +AHs-2 point+AH0- +AFs-AFP level: +ACY-le+ADs- 100 +AHs-0 point+AH0-, 100+ACY-ndash+ADs-1000 +AHs-2 point+AH0-, +ACY-gt+ADs- 1000 +AHs-3 point+AH0AXQ-), AFP-TTD criteria (AFP +ACY-le+ADs- 400 ng/mL +ACY-nbsp+ADs-and total tumor diameter +ACY-le+ADs- 8 cm), Malatya criteria (largest tumor diameter +ACY-le+ADs- 6 cm and AFP +ACY-le+ADs- 200 ng/mL and GGT+ACY-le+ADs- 104 U/L and +ACY-nbsp+ADs-well/moderate +ACY-nbsp+ADs-tumor differatiation), Extended Malatya criteria (within +ADw-i+AD4-vs+ADw-/i+AD4- beyond), 5-5-500 rule (nodule size +ACY-le+ADs-5 cm in diameter, nodule number +ACY-le+ADs-5, and +ACY-nbsp+ADs-AFP +ACY-le+ADs-500 ng/mL), Samsung criteria (+ACY-le+ADs- 7 tumors, diameter +ACY-le+ADs- 6 cm, AFP +ACY-le+ADs- 1000 ng/mL), macrovascular invasion (present, absent), tumor differentiation (well, moderate, poor), lympho-vascular invasion (present, absent), perineural invasion (present, absent), capsular invasion (present, absent),, tumor necrosis (present, absent), locoregional therapy (transarterial radioembolization +AFs-TARE+AF0-, +ACY-nbsp+ADs-transarterial chemoembolization +AFs-TACE+AF0-, radiofrequency ablation

+AFs-RFA+AF0-, microwave ablation +AFs-MWA+AF0-, resection etc), ascites (no, moderate, massive), outcome (alive, dead), recurrence (yes, no)+ADw-/p+AD4-

+ADw-p+AD4-Evaluation of Patients with HCC Who are Candidates for LT before the COVID-19 Pandemic+ADw-br /+AD4-In our institution prior to defining the Malatya criteria +AFs-32+AF0-, patients were considered as eligible to live donor liver transplantation only if the disease was confined to liver and without any macrovascular invasion. Since 2016, the indication for LT is discussed in multidisciplinary medical committee that is 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 (MSCT) scans, magnetic resonance imaging (MRI), and recently we also added positron emission tomography/computerized tomography scan (PET/CT) to our work-up scheme.+ADw-/p+AD4-

+ADw-p+AD4-Evaluation of Patients with HCC that are Candidates for LT during the COVID-19 Pandemic+ACY-nbsp+ADsAPA-br /+AD4AJg-nbsp+ADs-After the confirmation of the first case with COVID-19 in Turkey, the Ministry of Heath released new regulations limiting all the elective procedures including elective liver transplantations and advised the liver transplant centers to perform a risk stratification. Besides, emergency liver transplantations such as those performed for acute liver failure, recipients with a MELD score +ACY-gt+ADs- 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 are taken at the operating room and the patient ward. We have previously published our COVID-19 surveillance strategy in LDLT +AFs-31+AF0-. In the initial stages of the pandemic, patients with HCC within

Milan criteria and have tumors greater than 2 cm were transplanted.+ACY-nbsp+ADsAPA-br /+AD4-However, various vaccines have been developed and normalization efforts have started in countries who have vaccinated more than 70+ACU- 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, liver transplantation 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 liver transplantation.+ACY-nbsp+ADsAPA-/p+AD4-

+ADw-p+AD4-Our follow-up protocol after liver transplantation+ACY-nbsp+ADsAPA-br /+AD4-Our immunosuppressive treatment protocol following liver transplantation for HCC is as follows+ADs- corticosteroids are initiated stating from the completion of hepatic artery anastomosis and continues to the postoperative period. The dose is tapered gradually and discontinued on the postoperative 3rd to sixth month. Tacrolimus is initiated on the postoperative 3rd 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. On postoperative 1st month, the 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 liver transplantation tacrolimus-everolimus combination is continued.+ADw-br /+AD4-Our postoperative surveillance program is very intense. In the postoperative first 2 years, the AFP levels are analyzed every month. MSCT is obtained every three months for the first postoperative 2 years. Surveillance of the AFP levels are performed monthly in the follow-up period. After the second year following the liver transplantation, cross-sectional imaging techniques are performed annually. If there is a suspicion of recurrence on laboratory and MSCT, contrast enhanced MRI and PET CT are performed to confirm the diagnosis. In patients with hepatic recurrence, we perform multimodality treatment including resection,

locoregional therapeutic (LRT) options (transarterial therapies, radiofrequency or microwave ablations) and systemic chemotherapy including sorafenib. +ACY-nbsp+ADsAJg-nbsp+ADsAPA-/p+AD4-

+ADw-p+AD4-Statistical Analysis+ADw-br /+AD4-The statistical analyses were performed using IBM SPSS Statistics v25.0 (Statistical Package for the Social Sciences, Inc, Chicago, IL, USA). The quantitative variables were expressed as Median and Interquartile Range (IQR). +ACY-nbsp+ADs-The qualitative variables were reported as number and percent (+ACU-). +ACY-nbsp+ADs-Kolmogorov+ACY-ndash+ADs-Smirnov were used to assess normality of quantitative variables+ACY-rsquo+ADs-distribution. Nonparametric Mann Whitney-U test was used to compare quantitative variables. Pearson+ACY-rsquo+ADs-s chi-square test was used to compare qualitative variables. P +ACY-le+ADs- 0.05 was considered statistically significant value.+ACY-nbsp+ADsAPA-/p+AD4APA-/html+AD4-

RESULTS

General characteristics of the patients

In total 109 patients are included for analysis in the study and the median age of the patients in the study was 56 (IQR=15). Ninety-seven patients (89%) were male and 12 were female (11%). The common etiologies of liver disease were HBV (n = 52), cryptogenic (n = 26), HCV (n = 8), HBV+HDV (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 LRT. 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, 69 patients (69.9%) were within Malatya criteria and 75 patients (68.8%) were within the extended Malatya criteria. Seventeen patients (15.6%) had micro vascular invasion, 21 patients (19.3%) had poor differentiation, 46 patients (42.6%) had lympho-vascular 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 days (IQR=457; min-max= 17-1051 days). Fifteen patients (13.8%) died during the median follow-up period and 6 of the mortalities were within the postoperative first 90 days which was regarded as early mortality.

Pre-pandemic *vs* COVID-19 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 COVID-19 period underwent liver transplantation 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), BMI (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), WBC (P = 0.298), Hb (P = 0.079), platelets (P = 0.363), neutrophil (P = 0.394), lymphocyte (P = 0.498), NLR (P = 0.819), PLR (P = 0.634), INR (P = 0.112), creatinine (P = 0.955), albumin (P = 0.888), total bilirubin (P = 0.138), direct bilirubin (P = 0.306), AST (P = 0.157), ALT (P = 0.944), GGT (P = 0.213), LDH (P = 0.325), CRP (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, statistical significant difference was found between groups in terms of blood ALP levels (P = 0.029), lympho-vascular invasion (P = 0.019) and type of the liver graft that is transplanted (P = 0.017). In patients who were transplanted for HCC in the COVID-19 period, the use of grafts from the living donors 13.3 times more frequent

than the COVID-19 period (OR=13.3; 95%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 are operated during the COVID-19 period (OR=2.54; 95%CI=1.15-5.56). Categorical and continuous variables of the groups and results of the statistical analyses are summarized in Table-1 and Table-2.

DISCUSSION

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and also 4th to 5th leading cause of cancer-related death [33]. HCC usually develops in patients with chronic liver disease and viral hepatitis such as hepatitis B and C viruses play an important etiologic role in its development. Besides the incidence is rising in developed countries [34]. It meets the criteria of a particular disease that necessitates screening; 1) It is common in individuals of certain sub-population, 2) Population at highest risk of developing HCC is defined in detail 3) Screen 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, 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 clinico-pathologic characteristics in patients who were transplanted for HCC. This is one of the first studies evaluating the consequences of pandemic era on critical diseases such as HCC using the clinico-pathologic characteristics.

Various diseases such as cancer needs special attention for it is progressive nature which is especially valid if appropriate treatment is not applied; and, it leads to mortality [37]. On the other hand, the patients with a high risk for mortality due to 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]. European Society for Medical Oncology (ESMO) consensus statement states 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 and colleagues [41] have published their altered protocol for management of patients with end-stage liver disease including HCC. They have prioritized LT of HCC patients with 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 and colleagues [38] have published the results of this altered protocol in a brief communication. They have shown 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 have transplanted patients with HCC with tumor 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 is 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 lympho-vascular invasion was higher in patients transplanted during the COVID-19 period. We believe this may be related with the observational difference between the two time periods because the staging of the tumors (performed by different classification methods) were similar between the two groups and we have summarized these results in Table-1. Especially microscopic vascular invasion is a major determinant of early recurrence following treatment as well as a major risk factor for metastatic disease [42]. The patients operated 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 and colleagues [43] have shown that ALP and GGT were prognostic indictors in patients with HCC undergoing liver resection. Their cohort included 469 pathologically confirmed HCC. They have found that high ALP levels (≥136.5 IU/mL) were associated with larger tumors (> 5cm), vascular invasion, and advanced BCLC stages [43]. Also, they found that ALP was independent prognostic factor determining overall survival but not disease free survival [43]. Both Wu and colleagues, and other researchers have stated that GGT can be a marker for tumor stem cells, microvascular invasion, tumor proliferation, and nuclear cell cycle control in the tumors [43-46]. 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 which is a subjective parameter does not determine the absolute outcome of the tumors of the patients. We have also evaluated multiple parameters which 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 [45-56]. Aubert and colleagues [57] have performed a multi-institutional study and have shown that there was a dramatic decrease in both DDLT and LDLT activities [57]. Furthermore, in countries such as Japan the number of COVID-19 were low as well as COVID-19 related deaths and due to strict preventive measures taken there was nearly 70% decrease in solid organ transplantation [57]. However, in countries such as United States of America, the number of COVID-19 cases were higher as well as the number of deaths; but the there was only 4% decrease in solid organ transplantation [57]. In our institute, the DDLT rates decreased. However, we managed to preserve relatively high rate of LDLT, which is very unique when considering the study performed by Aubert

and colleagues. This is the reason why 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. This trend has not hanged during the pandemic era. Since the relatives are determined to donate their organs for their relatives, the LDLT was sustained in 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 are not considered. Since our study is not designed as an intention to treat analysis, we cannot draw definitive conclusions regrading 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

+ADw-html+AD4APA-p+AD4-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 rates in Turkey are already low and it further decreased during the pandemic. However, we managed to preserve 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.+ACY-nbsp+ADsAPA-/p+AD4APA-/html+AD4-

ARTICLE HIGHLIGHTS

Research background

COVID-19 has overwhelmed the health-care services all around the world. The organization of the 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.

Research motivation

COVID-19 has overwhelmed the health-care services all around the world. . Treatment of many cancer diseases such as liver cancers have been postponed until the COVID-19 pandemic was under control.

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 aim 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, clinico-pathological 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 and12 were female (11%). The most common etiology of liver disease was HBV (n = 52, 47.7%). Statistical significant difference was

found between groups in terms of blood ALP levels (P = 0.029), lympho-vascular invasion (P = 0.019) and type of the liver graft that is transplanted (P = 0.017). In patients who were transplanted for HCC in the COVID-19 period, the use of grafts from the living donors 13.3 times more frequent than the COVID-19 period (OR=13.3; 95%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 are operated during the COVID-19 period (OR=2.54; 95%CI=1.15-5.56).

Research conclusions

This study 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.

Research perspectives

+ADw-html+AD4APA-p+AD4-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 rates in Turkey are already low and it further decreased during the pandemic. However, we managed to preserve 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.+ACY-nbsp+ADsAPA-/p+AD4APA-/html+AD4-

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