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Effect of COVID-19 Pandemic on Hepatocellular Carcinoma Diagnosis: Results from a Single Turkey Center Study

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ABSTRACT

Background & Aims: Currently malignancies of the liver are the sixth most frequently diagnosed cancers worldwide. The admission of patients to hospitals decreased due to the restriction of the Coronavirus disease 2019 (COVİD-19) pandemic, especially patients suspected with cancer were delayed in their diagnosis and treatment. With this study, we aimed to investigate whether the Covid-19 pandemic caused a decrease in the number of hepatocellular cancers (HCC) or a delay in its diagnosis.

Methods: The study, which included newly diagnosed HCC patients, was conducted as a retrospective cross sectional study, in a single Turkey medical center. The patients were divided into pre-COVID-19 and post-COVID-19 two-year periods and compared in terms of tumor size, biochemical parameters, clinical and demographic features.

Results: A total of 63 HCC patients, 46 (73%) patients before the COVID-19 pandemic and 17 (27%) patients diagnosed during the COVID-19 pandemic were included. Maximum diameter of lesions and serum alpha-fetoprotein levels showed a statistically significant difference between the groups. Maximum tumor size in the pre-COVID-19 period was 4.58±3.77 mm, while in the COVID-19 period was 7.42±6.88 mm, the difference between two groups being statistically significant ($p<0.05$). HCC in the pre-COVID-19 period were detected mostly at Barcelona Clinic for Liver Cancer (BCLC) stage A (45.7%, n=21), while in the COVID-19 period most of HCC were detected at stage B (35.3%, n=6).

Conclusions: The COVID-19 pandemic limited the access of patients to screening programs for HCC. The significant disruption in screening cirrhotic patients for HCC has led to a delay in diagnosis.

Key words: hepatocellular carcinoma – HCC – COVID-19 – pandemic – cancer – diagnosis – screening.

Abbreviations: BCLC: Barcelona Clinic for Liver Cancer; COVID-19: coronavirus disease 2019; HCC: hepatocellular carcinoma.

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INTRODUCTION

One of the most frequently diagnosed cancers in the world is liver cancer; it is the sixth most frequently detected tumor, approximately 905,677 new cases were reported in 2020. In addition, liver cancer is the third most common cause of cancer-related mortality worldwide, with over 830,180 deaths in 2020 [1].

During the coronavirus disease 2019 (COVID-19) pandemic, suspension of elective non-emergency medical services was imposed all over the world. As a result of this, many patients could not get access to medical services which led to the delay in the diagnosis and treatment of various diseases.

The cancer screening programs have been temporarily interrupted worldwide during the pandemic. These measures may have led to a reduction in COVID-19 transmission, but it is thought that the delayed diagnoses of cancer patients will put an additional burden on the global health system.

The aim of this study was to reveal whether restrictions during the COVID-19 pandemic led to reductions or delays in the diagnosis of hepatocellular cancer (HCC).

METHODS

Study Design and Patient Data Source

This study was designed as a single center, cross-sectional and retrospective study including adult patients with a new

diagnosis of hepatocellular carcinoma (HCC). Based on March 11, 2020, the date of the first COVID-19 case in Turkey, the observation period was divided into the pre-COVID-19 and COVID-19 periods.

Patients were divided into two groups; patients with a new diagnosis of HCC during pre-COVID-19 period (March 2017 – February 2020) and patients with a new diagnosis of HCC during the COVID-19 period (March 2020 - March 2023). The multidisciplinary council for patients with HCC diagnosis was held at our clinic between 2017-2023 with the participation of general surgeons, oncologists, and gastroenterologists. Medical records and data of the patients were collected from the multidisciplinary council meeting decisions and hospital records. The date of discussion of the patients in the multidisciplinary council was taken as a reference point for the date of diagnosis of HCC, hence conferring the patient to the pre-COVID-19 and COVID-19 periods.

Date of diagnosis, general demographics, main tumor size, extrahepatic disease, Barcelona Clinic Liver Cancer (BCLC) stage, serum alpha-fetoprotein level, adherence to surveillance, underlying disease etiology, presence of tumor thrombosis and treatment were recorded.

Inclusion Criteria

Adult patients (≥18 years) diagnosed with HCC. The diagnosis of HCC was determined histologically or by dynamic imaging according to the European Association for the Study of the Liver (EASL) Guidelines [2].

Statistical Analysis

Statistical analyses of all data, were performed using SPSS statistics version 21 (SPSS Inc.,Chicago, IL, USA). All variables were assessed for normality using the Kolmogorov-Smirnov/ Shapiro–Wilk test. Categorical variables were shown as numbers (n) and proportions (%) of patients and continuous variables were reported as mean±standard deviation (SD) or median. Differences between continuous datasets were assessed with unpaired t-tests and Mann-Whitney U tests for parametric and non-parametric datasets, respectively. comparison the analysis for categorical variables between independent groups Pearson chi-square test or Fisher exact test was selected as appropriate. P values < 0.05 were considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Committee of Gazi University Hospital. All data were processed by accessing the hospital database, which only researchers can access.

RESULTS

A total of 72 patients with de-novo HCC diagnosis were collected. During the pre-COVID-19 period there were 46 new HCC diagnoses compared with 26 new HCC diagnoses in the COVID-19 period. Detailed patient characteristics and clinical features are shown in Table I.

The median ages were 62.95±10.30 and 64.61±9.01 respectively in pre-COVID-19 period and COVID-19 period. Pre-COVID-19 period included 37 men (80.4%) and COVID-19 period included 24 men (92.3%). There were no significant differences in gender distribution (p=0.179) or median age (p=0.495) between the two groups. When cases were analyzed according to etiology, there were no significant differences overall. In terms of etiology, the most common etiologic cause was chronic viral hepatitis B infection in both groups [pre-COVID-19 and COVID-19 period, respectively 60.9% (n=28); 56.9% (n=13)]. Patients in the pre-COVID-19 period were most frequently diagnosed in BCLC A stage (45.7%, n=21), while in the COVID-19 period, they were most frequently diagnosed in BCLC B stage (50%, n=13) ECOG stage 0 was mostly seen in both groups [pre-COVID-19 (50%, n=23) and COVID-19 period (61.5%, n=16)] There were no significant differences in BCLC stage (p=0.095) or ECOG stage (p=0.262) between the two groups.

In the pre-COVID-19 period 8.7% (n=4) patients and in the COVID-19 period 30.7% (n=8) were diagnosed with portal vein thrombosis, the difference being statistically significant (p=0.042).

In terms of extrahepatic metastasis there was no statistically significant difference between the two groups [p=0.117, n=4 (8.7%) pre-COVID-19 period and n=6 (23.1%) COVID-19 period].

A total of 38 (82,6%) patients had cirrhosis in the pre-COVID-19 period, while 22 (84.6%) patients had cirrhosis in the COVID-19 period. There was no statistically significant difference between the groups in terms of cirrhosis incidence (p= 0.826). Most patients with HCC in both pre-COVID-19 and COVID-19 period were diagnosed in Child-Pugh A stage and there was no statistically significant difference between the groups (p=0.892).

There was no statistically significant difference between the groups in terms of serum albumin level, Child–Pugh score and MELD score (p=0.302;0.799 and 0.165 respectively) (Table I). The largest tumor diameter and serum AFP levels were found to be statistically significantly higher in the COVID-19 period than in the pre-COVID- 19 groups (p=0.009; 0.005, respectively).

The proportion of patients receiving local treatments (transarterial radioembolization; transarterial chemo-embolization; radiofrequency ablation) was 54.3% (n=25), and 50.0% (n=13) in pre-COVID-19 and COVID-19 period respectively. While liver transplantation was performed in only one patient during the COVID-19 period, two liver transplantation were done during the pre-COVID-19 period.

Resection of HCC was performed on 21.7% (n=10) and 3.8% (n=1) of patients in the pre-COVID-19 and COVID-19 period, respectively. A higher proportion of patients required systemic chemotherapy in the COVID-19 period. While systemic chemotherapy were given to 15.2% (n=7) of patients in the pre- COVID-19 period, 30.8% (n=8) of the patients in the COVİD-19 period received chemotherapy. The palliative treatment was given for 2 (4.3%) patients in the pre- COVID-19 period and 2 (7.7%) in the COVID- 19 period. There were no significant differences in the types of treatments between the two groups (p=0.189).

Table I Demographic, clinical and paraclinical characteristics

	Pre-COVİD-19 N=46	COVİD-19 N=26	p
Age (year)	62.95±10.30	64.61±9.01	0.495
Male, n (%)	37 (80.4)	24 (92.3)	0.179
Etiology, n (%)			0.647
HBV	28 (60.9)	13 (50.0)	
HCV	5 (10.9)	2 (7.7)	
NASH	4 (8.7)	2 (7.7)	
Alcohol	2 (4.3)	3 (11.5)	
Cryptogenic	6 (13)	6 (23.1)	
Tyrosinemia	1 (2.2)	0 (0.0)	
Cirrhosis, n (%)	38 (82.6)	22 (84.6)	0.826
Child-Pugh classification, n (%)			0.892
A	22 (47.8)	13 (50.0)	
B	12 (26.1)	5 (19.2)	
C	5 (10.9)	4 (15.4)	
Child-Pugh score	6 (5-13)	6 (5-14)	0.799
MELD score	10 (7-31)	11 (7-27)	0.165
Barcelona stage, n (%)			0.095
0	5 (10.9)	2 (7.7)	
A	21 (45.7)	4 (15.4)	
B	13 (28.3)	13 (50.0)	
C	5 (10.9)	5 (19.2)	
D	2 (4.3)	2 (7.7)	
Largest tumor diameter	3.90 (1.10-20.0)	6.75 (1.50-20.0)	**0.009**
AFP	11.81 (1.51-14290.0)	90.0 (2.10-629495.0)	**0.005**
Albumin	3.3 (3.0-4.5)	3.6 (4.0-4.8)	0.302
ECOG performance status, n (%)			0.262
0	23 (50.0)	16 (61.5)	
1	14 (30.4)	7 (26.9)	
2	8 (17.4)	1 (3.8)	
3	1 (2.2)	1 (5.9)	
4	0 (0.0)	1 (1.4)	
Portal vein thrombosis, n (%)	4 (8.7)	8 (30.7)	0.042
Extrahepatic involvement, n (%)	4 (8.7)	6 (23.1)	0.117
Treatment decisions, n (%)			0.189
Systemic chemotherapy	7 (15.2)	8 (30.8)	
Palliative treatment	2 (4.3)	2 (7.7)	
Local treatment (TARE, TACE, RF)	25 (54.3)	13 (50.0)	
Liver transplantation	2 (4.3)	2 (7.7)	
Resection	10 (21.7)	1 (3.8)	

Categorical datasets have been analyzed by the t-test and chi-square test. HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis; ECOG: Eastern Cooperative Oncology Group; TARE: transarterial radioembolization; TACE: transarterial chemoembolization; RF: radiofrequency ablation.

DISCUSSION

This is the first study in Turkey to compare groups with newly diagnosed HCC before and during the COVID-19 pandemic. Although the effect of short-term temporary restrictions in controlling the pandemic are very effective, we postulated that it may increase morbidity in the long-term by reducing the frequency of patients in the follow-up.

Routine cancer screenings were temporarily stopped during the pandemic, and the follow-up intervals were extended. Cancer diagnosis rates have decreased during the pandemic because of stay-at-home orders, avoidance of going to the

hospital for fear of infection and restricting people's access to health services. Unfortunately, the consequence of the interruption of cancer screening and follow up may have shifted the diagnosis of cancer towards a more advanced stage and increased the overall mortality of those patients also.

In early March 2020, it was announced that the first COVID-19 case was detected in Turkey. Social distancing and home confinement are two restrictions instituted by our government during the COVID-19 pandemic. Also, complete lockdowns have been implemented to control the spread of the disease occasionally during the pandemic. To reduce transmission risk some short time adjustments were accommodated by healthcare providers such as delaying the screening programs and elective surgical treatments and suspension of face-to-face visits [3-6].

Many restrictions related to the pandemic such as stay-at home orders were lifted in June 2020 across the country, but people had still hesitations to apply for health care. Both the restriction of access to health services implemented by the government and tendency of people due to fear of infection led to the delay of routine check-ups and follow ups. This may have been resulted in the delayed diagnosis of de-novo cancers or disrupted the follow up of cancer patients leading to increased mortality due to above mentioned reasons [7, 8].

Several studies have demonstrated the impact of COVID-19 on cancer screening programs. Maringe et al. [9] have recently shown that delays in the diagnosis and treatment may have increased mortality of breast, colorectal, and lung cancers by as much as 9.6%, 16.6%, and 5.3%, respectively, after 5 years in United Kingdom. Granier et al. [10] described a significant association between decreasing screening numbers in breast, colon, prostate, and lung cancer and COVID-19 pandemic in the USA [10].

İn this study, both the mean HCC tumor size and rates of portal vein thrombosis on initial presentation significantly increased during the COVID-19 period. The consequences of advanced stage and complicated HCC will have a negative impact on the overall mortality of patients, and it will lead to increased health expenditures. These findings are largely in line with a similar study performed by Gandhi et al. [11]. In their multi-center analysis, they compared HCC stages during the pre-pandemic and COVID-19 period. They found a significant delay in the diagnosis of de-novo HCC cases, a delay in initiating HCC treatment and an increase in complications rates [11].

The limitation of this study is that it is a retrospective-single-center study with limited sample size. The findings may not be generally applicable to other patient populations because of being a single-center study and because of the relatively small number of patients. Future research should focus on long term follow up with a larger number of patients for further evaluation of COVID-19 pandemic consequences.

CONCLUSIONS

The current study showed that, with the strict measures taken to keep the COVID-19 pandemic under control, we encountered HCC patients at more advanced stages and complications.

To minimize the negative impact of the pandemic such as an increase of avoidable advanced cancers and cancer-related deaths, post-pandemic management should focus on improving the number of screening programs and encouraging patients to strictly adhere to visits in the follow-up.

Conflicts of interest: None to declare.

Authors' contribution: G.B.,N.E.,M.K. and T.K. designed the study. G.B.,S.Ö.,K.M.,H.K.,S.D. and A.A. collected the data.G.B. and N.E. provided the statistical analysis, drafted the manuscript and revised it. M.K. revised it critically for the scientific content. All the authors read and proved the final version.

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