Characteristics of Newly Diagnosed Hepatocellular Carcinoma Patients Across Turkey: Prospective Multicenter Observational 3K Registry Study

Ulus Salih Akarca[1], Belkis Unsal[2], Orhan Sezgin[3], Kendal Yalcin[4], Meral Akdogan[5], Can Gonen[6], Feyza Gunduz[7], Seren Ozenirler[8], Abdullah Sonsuz[9], Dinc Dincer[10], Salim Basol Tekin[11], Idris Yucel[12], Hakan Akbulut[13], Canan Alkım[14], Ozgur Ozyilkan[15], Arzu Baygul[16], Zeynep Merve Cevik[17], Ramazan Idilman[18] on behalf of 3K Registry Study Group

[1]Department of Gastroenterology, Ege University Faculty of Medicine, Izmir, Turkey
[2]Clinic of Gastroenterology, Izmir Ataturk Training and Research Hospital, Izmir, Turkey
[3]Department of Gastroenterology, Mersin University Faculty of Medicine, Mersin, Turkey
[4]Department of Gastroenterology, Dicle University Faculty of Medicine, Diyarbakir, Turkey
[5]Clinic of Gastroenterology, Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey
[6]Clinic of Gastroenterology, Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey
[7]Clinic of Gastroenterology, Marmara University Faculty of Medicine Pendik Training and Research Hospital, Istanbul, Turkey
[8]Department of Gastroenterology, Gazi University Faculty of Medicine, Ankara, Turkey
[9]Department of Gastroenterology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey
[10]Department of Gastroenterology, Akdeniz University Faculty of Medicine, Antalya, Turkey
[11]Department of Oncology, Ataturk University Faculty of Medicine, Erzurum, Turkey
[12]Department of Oncology, Ondokuz Mayis University Faculty of Medicine, Samsun, Turkey
[13]Department of Oncology, Ankara University Faculty of Medicine, Ankara, Turkey
[14]Clinic of Gastroenterology, Sisli Etfal Training and Research Hospital, University of Health Sciences, Istanbul, Turkey
[15]Department of Oncology, Adana Baskent University Faculty of Medicine, Adana, Turkey
[16]Department of Biostatistics, Koc University School of Medicine, Istanbul, Turkey
[17]Medical Management, Bayer Türk, Istanbul, Turkey
[18]Department of Gastroenterology, Ankara University Faculty of Medicine, Turkey

Cite this article as: Salih Akarca U, Unsal B, Sezgin O, *et al*. Characteristics of newly diagnosed hepatocellular carcinoma patients across turkey: prospective multicenter observational 3K registry study. *Turk J Gastroenterol*. 2021;32(12):1019-1028.

ABSTRACT

Aims: *To evaluate patient profile for epidemiological and clinicopathological characteristics and potential risk/prognostic factors in newly diagnosed hepatocellular carcinoma (HCC) patients across Turkey.*

Methods: *A total of 547 patients (mean (SD) age 62.6 (10.3) years, 81.9% were males) were included in this registry study. Data on patient characteristics, etiologies of HCC, laboratory values, and tumor characteristics and stages were recorded at study enrollment.*

Results: *HBV infection (68.2%) was the leading etiology, followed by HCV infection (17.2%), HDV infection (5.5%), alcohol (6.4%), and NAFLD (3.5%), as the major etiologies. Considering that 51.6% of the patients had >5 cm HCC, 44% were Child–Pugh B/C and 57% were BCLC B-D, it appears that a significant group of HCC patients were diagnosed at advanced stages. Of 540 patients, 271 (50.2%) were referred or applied with the diagnosis of HCC. Patients with HCC at presentation had larger tumor size (median (min-max) 6.6 (0-30) vs. 4.8 (0-90) cm, P < .001) and more advanced BCLC stage (Stage C-D in 40.8% vs. 26.4%, respectively, P = .005), compared to patients who were diagnosed during follow-up.*

Conclusions: *Our findings revealed that HBV infection was the leading etiology and a moderate-to-advanced disease was evident in more than half of patients at the time of diagnosis. HCC patients diagnosed at follow-up had smaller tumor size and earlier BCLC stage.*

Keywords: *Hepatocellular carcinoma, epidemiology, risk factors, prognostic factors, screening, Turkey*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common tumor and the third cause of cancer-related death in the world.[1] Despite a tendency toward an improved survival in the past 2 decades, possibly related to earlier detection of tumors at a curative stage via preventive and screening strategies,[2] the prognosis of HCC still remains very poor.[3]

Moreover, HCC has been associated with unfavorable trends in several areas of the world and with the largest increase in incidence among all malignancies over the past

Corresponding author: ***Ulus Salih Akarca****, e-mail:* ***ulusakarca@gmail.com***
Received: ***January 9, 2021*** *Accepted:* ***May 3, 2021*** *Available Online Date:* ***November 26, 2021***

DOI: ***10.5152/tjg.2021.201171***

decade.[4] The increase in incidence despite the reducing incidence of chronic hepatitis infections has been linked to changing liver cancer epidemiology, with a growing role of liver metabolic disorders including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in the etiology of HCCs as the new precancerous conditions.[5]

Given that currently available medical therapies offer only marginal survival benefit once the disease progresses into an incurable advanced-stage disease,[6] the awareness of HCC risk factors and screening for early tumor detection in patients at risk are considered to be of utmost importance to be able to apply a curative treatment and improve survival.[6,7]

According to Turkey Cancer Statistics in 2016, age-adjusted HCC rate (per 100000 people) was reported to be 4.3 in men and 1.8 in women.[8] HCC is known to have a considerable geographic variability in etiology, epidemiology, target population, and staging, as well as in transplant eligibility,[9] emphasizing the potential of epidemiological and local data on the profile and management of HCC patients to guide physicians on the best treatment methods to extend survival, and create awareness among health authorities and population to control risk factors.

This observational multicenter registry study was therefore designed to evaluate patient profile, epidemiological and clinicopathological characteristics and potential risk/prognostic factors in newly diagnosed HCC patients across Turkey. We aimed to increase awareness of the clinicians by providing local data on HCC patient profile along with the risk/prognostic factors evident at the time of initial diagnosis to improve future HCC screening practice as well as practice patterns.

MAIN POINTS

- *HBV infection was the leading etiology and a moderate-to-advanced disease was evident in more than half of the newly diagnosed HCC patients at the time of diagnosis.*
- *Prior to HCC diagnosis, half of the patients were previously diagnosed with cirrhosis or hepatitis.*
- *Referral patients directly diagnosed with HCC had larger tumor size and more advanced BCLC stage.*
- *There is a need for increased awareness among clinicians for HCC risk factors and of the utility of HCC surveillance among high-risk patients with hepatitis or cirrhosis to enable early disease detection and implementation of potentially curative treatment.*

METHODS

Study Population

A total of 547 patients with newly diagnosed HCC were included in this prospective multicenter non-interventional epidemiological registry study conducted at 25 different tertiary care gastroenterology and oncology clinics across Turkey. The patients were enrolled between September 2012 and July 2015 and were followed up until September 2017. Adult (≥18 years of age) patients diagnosed with HCC within the past 3 months were included in the study. Lack of sufficient baseline data, presence of any situation/condition that would significantly complicate patient follow-up according to investigator's opinion, and current or previous participation in another observational study were the exclusion criteria of the study.

Written informed consent was obtained from each patient following a detailed explanation of the objectives and protocol. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by institutional ethics committee.

Data Collection

Data on patient demographics (age, gender), anthropometrics [weight (kg), height (cm), body mass index (BMI; kg/m^2)], smoking status, alcohol consumption, family history for hepatitis and HCC, other malignancies, previous blood transfusion, comorbidities, etiology of HCC, admission symptoms, diagnostic methods, viral load (if available, HBVDNA, HCVRNA, HDVRNA), HCV genotype, alpha-fetoprotein (AFP; ng/dL) levels, distant metastasis, tumor characteristics (morphology, size, TNM staging), number of liver lesions, Eastern Cooperative Oncology Group (ECOG) performance status, Child–Pugh Scoring and Barcelona Clinic Liver Cancer (BCLC, 2011) stage were recorded at study enrollment. After the study enrollment (registry visit), patients were followed every 3 months for at least 2 years. In accordance with the non-interventional design, selection of treatment approach and timing of follow-up visits were at the physicians' discretion and applied according to the local prescribing information and routine medical practices.

The current study evaluated data on patient profile, epidemiological and clinicopathological characteristics, and potential risk and prognostic factors recorded at the time of initial diagnosis. Follow-up data on effectiveness and safety of treatments in relation to epidemiological characteristics and prognostic factors and survival outcome are presented elsewhere.

Statistical Analysis

Based on annual incidence of HCC (2217 patients per year) in Turkey,[10] sample size was calculated to include at least 546 patients to represent the estimated number of 6651 HCC cases to occur over the 3-year study period with 5% margin of error in a 95% CI and at 50% lost-to-follow-up ratio. However, as the study was a non-interventional epidemiological registry study, and the participating centers registered patients eligible by the inclusion/exclusion criteria. Due to the observational study design and lack of hypothesis to be tested, sample size was not restricted, and the target was raised to 1000 patients by the potential of study sites. Overall, 574 patients were enrolled into the study and 27 patients were excluded from the analysis due to drop-outs.

Statistical analysis was performed by using the software package MedCalc Statistical Software, version 12.7.7 (MedCalc Software Bvba, Ostend, Belgium). Descriptive analysis of the data was performed using summary statistics for categorical and quantitative (continuous) data. Data were expressed as mean (standard deviation, SD), median (minimum-maximum) and percent (%) where appropriate. Valid percentage was used for descriptive analysis while missing data were included for nominal variables.

RESULTS

Patient Demographics and Clinical Risk Factors

The mean patient age at diagnosis was 62.6 years (range, 19 to 92 years, 72.5% aged 40-69 years) and males composed 81.9% of the study population (Table 1).

Overall, 37.8% and 15.5% of patients were in the overweight (25-30 kg/m^2) and obese (>30 kg/m^2) categories, while current and previous regular alcohol consumption was noted in 7.7% and 19.0% of patients, respectively (Table 1).

Positive family history for hepatitis was evident in 27.9% and 10.9% of HBV and HCV patients, respectively. Family history for HCC was evident in 6.3% of patients (first-degree relatives in 72.4%) (Table 1).

Previous history of blood transfusion was evident in 15.4% of patients. Comorbid diseases were noted in 45.6% of patients (hypertension in 29.6% and diabetes mellitus in 22.9%) (Table 1).

Etiology, Admission Symptoms, and Diagnosis of HCC

HBV infection (68.2%) was the leading etiology, followed by HCV infection (17.2%), HDV infection (5.5%), alcohol (6.4%), and NAFLD (3.5%), as the major etiologies (Table 2).

The 3 most common symptoms on admission were abdominal pain (28.2%), abdominal swelling (23.1%), and weight loss (11.3%) (Table 3).

The most common methods used in diagnosis of HCC were magnetic resonance imaging (MRI, 62.2%), ultrasound (US, 45.7%), and computed tomography (CT, 43.9%), while biopsy was performed in 13.5% of patients and PET-CT in 4.9% of patients.

Overall, 269 (49.8%) patients were under follow-up with former diagnosis of cirrhosis or chronic liver disease, while HCC was the first diagnosis in 271 (50.2%) patients. Median viral load for HBV-DNA (n = 165), HCV-RNA (n = 46), and HDV-RNA (n = 5) were determined to be 4.0 log10 IU/mL (range, 0.0 to 8.8), 5.6 log10 IU/mL (range, 1.5 to 8.7) and 4.1 log10 IU/mL (range, 1.6 to 6.6), respectively. Genotype 1 (96.0%) was the most prevalent HCV genotype among patients with available data on genotyping (n = 25).

Tumor Characteristics

Most patients presented with tumors with nodular morphology (79.3%) and size of 3-8 cm (50.0%) along with T1-T2 (56.4%), N0 (41.4%), and M0 (43.3%) staging characteristics. Presence of >3 nodules or diffuse HCC was noted in 17.4% of patients. According to overall TNM staging, Stage I HCC was evident in 43.2% of patients at the time of diagnosis, followed by Stage IIIA (21.4%) and Stage II (18.0%) tumors (Table 4).

The mean numbers of primary tumors and satellite lesions were 2.3 (range, 0 to 5) and 1.8 (range, 0 to 15), respectively. Distant metastasis was evident in 8.9% of patients (Table 4).

Prognostic Factors

The mean serum AFP level was 2.0 log10 ng/dL (range, 0 to 4.8), while AFP levels were ≤20 ng/dL in 38.0% of patients and >400 ng/dL in 32.2% of patients. The majority of patients were in ECOG performance status of 0 (42.7%) or 1 (40.1%). Child–Pugh scoring revealed 56.2% of patients to be in Class A category, as followed by Class B (33.5%), and Class C (10.5%) categories. At the time of

Table 1. Patient Demographics and Baseline Characteristics

Patient Demographics	
Gender, n (%)	
Male	448 (81.9)
Female	99 (18.1)
Age at diagnosis (years)	
Mean (SD)	62.6 (10.3)
Median (min-max)	63.0 (19.0-92.0)
Age groups, n (%)	
19-39 years	9 (1.6)
40-59 years	190 (34.8)
60-69 years	206 (37.7)
70-79 years	119 (21.8)
≥80 years	22 (4.0)
Body mass index (kg/m^2), mean (SD, min-max)	25.9 (4.4,16.1-44.4)
BMI category, n (%)	
<25 kg/m^2	255 (46.6)
25-30 kg/m^2	207 (37.8)
>30 kg/m^2	85 (15.5)
Comorbid diseases, n (%)[1]	236 (45.6)
Hypertension	129 (29.6)
Diabetes mellitus	100 (22.9)
CAD	46 (10.6)
COPD	14 (3.2)
Dyslipidemia	7 (1.6)
Other	140 (32.1)
Risk factors	
Smoking status, n (%)[2]	
Active smoker	101 (18.7)
Former smoker	200 (37.0)
Non-smoker	205 (37.9)
Package-year, mean (SD, min-max)	34.9 (12.0, 1.0-62.0)
Alcohol consumption, n (%)[3]	
Regular	42 (7.7)
Former	104 (19.0)
None	391 (71.5)
Duration (years), median (min-max) (n = 99)	25.0 (3.0-60.0)
Amount (units), median (min-max), (n = 102)*	15.0 (1.0-170.0)
Family history, n (%)[4]	
Hepatitis	
Total	122 (22.5)
In HBV + patients	83 (27.9)
In HCV + patients	10 (10.9)
HCC	
Total	32 (6.3)
First-degree relatives	21 (72.4)
Second-degree relatives	7 (24.1)
Spouse	1 (3.4)
Other malignancies	
Total	124 (25.9)
Lung	32 (25.8)
GIS	28 (22.6)
Hematological	11 (8.9)
Breast	8 (6.5)
Brain	8 (6.5)
Other	37 (29.8)
Blood transfusion, n (%)[5]	77 (15.4)

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease. Missing data for [1]29, [2]35, [3]10, [4]69, and [5]47 patients.

diagnosis, 32.9% of patients were in advanced (26.5%) or terminal (6.4%) disease stage according to the BCLC staging (Table 5).

Diagnosis, TNM Stage, and AFP Levels with Respect to BCLC Stage

Patients diagnosed with HCC at presentation had larger tumor size (median 6.6 vs. 4.8 cm, $P < .001$) and more advanced BCLC stage (Stage C-D in 40.8% vs. 26.4%, respectively, $P = .005$) when compared to patients with prior diagnosis of cirrhosis or hepatitis (Table 6).

BCLC stage C-D disease was noted in 11.5% of TNM Stage I patients and in 41.2% of TNM Stage II patients. AFP levels were significantly higher in BCLC stage C ($P < .001$ for each) and Stage D ($P < .01$ for each) disease as compared with BCLC stage 0 and B disease (Table 6).

Table 2. Etiology of Hepatocellular Carcinoma

Etiology of hepatitis, n (%)	
Viral hepatitis	
HBV infection	373 (68.2)
HCV infection	94 (17.2)
HDV infection	30 (5.5)
Alcohol	35 (6.4)
Non-alcoholic fatty liver disease	19 (3.5)
Cryptogenic liver disease	38 (6.9)
Autoimmune hepatitis	3 (0.5)
Primary/secondary biliary hepatitis	5 (0.9)
Wilson's disease	1 (0.2)
Other	8 (1.5)

HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus.

Table 3. Admission Symptoms of Hepatocellular Carcinoma

Symptoms at the Time of Referral, n (%)*	
Abdominal pain	235 (28.2)
Abdominal swelling	192 (23.1)
Weight loss	94 (11.3)
Jaundice	68 (8.2)
Nausea	63 (8.2)
Fatigue	47 (7.6)
Vomiting	37 (4.4)
Itching	29 (3.5)
Other	67 (8.1)
None	62 (11.3)

DISCUSSION

Our findings revealed a median of 63 years of age at the time of diagnosis and a male preponderance in newly diagnosed HCC patients, along with HBV-related etiology in most of the patients. The basic tumor characteristics involved nodular morphology, size of 3-8 cm, and TNM Stage I tumors in most of the patients. AFP levels were >400 ng/dL, and advanced to terminal stage (BCLC C to D) disease was evident in one-third of the study population, while Child–Pugh Class B to C liver damage was evident in almost half of the patients at the time of initial diagnosis.

In a recent single-center study conducted between 2001 and 2011 among 545 newly diagnosed HCC patients in Turkey, authors reported a male preponderance

Table 4. Tumor Characteristics

Tumor morphology (n = 511), n (%)	
Infiltrative	62 (12.1)
Nodular	405 (79.3)
Unknown	44 (8.6)
Size of the largest tumor (n = 190), n (%)	
<3 cm	42 (22.1)
3-5 cm	50 (26.3)
5-6.5 cm	24 (12.6)
6.5-8 cm	21 (11.1)
>8 cm	53 (27.9)
Number of primary tumors	
Total, mean (SD, min-max)	2.4 (1.0, 1.0-5.0)
≤3, n (%)	407 (82.6)
>3 or diffuse	86 (17.4)
Number of satellite lesions, median (min-max)	1.8 (1.9, 0.0-15.0)
Distant metastasis (n = 481), n (%)	43 (8.9)
TNM staging, n (%)	
Tumors (T) (n = 527)	
Tx	34 (6.5)
T0	110 (20.9)
T1	156 (29.6)
T2	141 (26.8)
T3	83 (15.7)
T4	3 (0.6)
Lymph node (N) (n = 522)	
Nx	273 (52.3)
N0	216 (41.4)
N1	33 (6.3)
Total	522 (100)
Metastasis (M) (n = 525)	
Mx	263 (48.1)
M0	237 (43.3)
M1	25 (4.6)
TNM stage (n = 206)	
Stage I	89 (43.2)
Stage II	37 (18.0)
Stage IIIA	44 (21.4)
Stage IIIB	16 (7.8)
Stage IVB	20 (9.9)

Tx, Nx, Mx, inability to assess.

Table 5. Prognostic Factors

Serum AFP Levels (n = 537)	
Log 10 ng/dL, mean (SD, min-max)	2.0 (1.3, 0-4.8)
Category, n (%)	
≤20 ng/dL	204 (38.0)
21-400 ng/dL	160 (29.8)
401-1000 ng/dL	53 (9.9)
>1000 ng/dL	120 (22.3)
ECOG performance status (n = 536), n (%)	
0	229 (42.7)
1	215 (40.1)
2	52 (9.7)
3	30 (5.6)
4	10 (1.9)
5	0
Child–Pugh Scoring (n = 511), n (%)	
Class A	287 (56.2)
Class B	171 (33.5)
Class C	53 (10.5)
BCLC stage (n = 517), n (%)	
0 (very early stage)	73 (14.1)
A (early stage)	150 (29.0)
B (intermediate stage)	124 (24.0)
C (advanced stage)	137 (26.5)
D (terminal stage)	33 (6.4)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group.

(82.0%) and median patient age of 60 years (range, 19 to 85), while HBV was the primary etiology (52.6%), followed by HCV (22.0%), cryptogenic liver disease (7.1%), hepatitis D (6.7%), alcoholic liver disease (3.9%), NAFLD (1.8%), and autoimmune liver disease (0.9%).[11]

The authors also reported presence of cirrhosis in the majority of patients at different stages including Child A (45.3%), Child B (25.7%), and Child C (16.5%), while BCLC stages were reported to include BCLC 0 (2.6%), BCLC A (27.9%), BCLC B (19.2%), BCLC C (21.1%), and BCLC D (29.2%) with extrahepatic metastasis in 4.8% of patients.[11]

The findings from the current study, conducted in the 2011-2016 period, are consistent with the 2001-2011 data previously reported in 545 Turkish HCC patients[10] in terms of patient demographics and prevalence of HBV, HCV, and HDV etiology. However, there was a tendency toward higher rates for alcoholic liver disease (7.5%), NAFLD (4.1%), and cryptogenic liver disease (8.2%), as well as a tendency for lower rates of advanced-terminal stage disease (32.9% vs. 50.3) and Child–Pugh C (10.5% vs. 16.5%) scores in our cohort. This may indicate the likelihood of changing epidemiology in Turkish HCC patients over time with higher likelihood of very early to intermediate stage of disease and milder liver damage at the time of diagnosis, as well as higher prevalence of liver metabolic risk factors in the cirrhosis etiology.

Table 6. Diagnosis, TNM Stage, and AFP Levels with Respect to BCLC stage

	BCLC Stage					
	0	A	B	C	D	*P*
Diagnosis[a]						
Directly with HCC (n = 271)	31 (12.3)	60 (23.8)	58 (23)	79 (31.3)	24 (9.5)	.005[1]
After cirrhosis or hepatitis (n = 269)	40 (15.3)	89 (34.1)	63 (24.1)	58 (22.2)	11 (4.2)	
TNM stage						
Stage I (n = 89)	10 (11.5)	49 (56.3)	18 (20.7)	10 (11.5)	0	-
Stage II (n = 37)	1 (2.9)	2 (5.9)	17 (50)	11 (32.4)	3 (8.8)	
Stage IIIA (n = 44)	3 (7)	1 (2.3)	9 (20.9)	26 (60.5)	4 (9.3)	
Stage IIIB (n = 16)	2 (12.5)	1 (6.3)	4 (25)	7 (43.8)	2 (12.5)	
Stage IVB (n = 20)	0	0	1 (5)	16 (80)	3 (15)	
AFP level, median (min-max)	1.5 (0-4.8)^{*,q}	1.3 (0-4.8)^{qq}	1.8 (0-4.8)^{*,q}	2.5 (–0.3-4.8)	2.9 (0-4.8)	<.001[2]

*P < .001 compared to BCLC stage C, qP < .01 and ^{qq}P < .001 compared to BCLC stage D.
[a]Missing data for 7 patients. [1] χ^2 test, [2] Kruskal–Wallis test (post hoc analysis, Mann–Whitney U-test with Bonferroni correction).

Notably, in a recent single-center study from Turkey regarding the changing epidemiology of chronic hepatitis C infection among 313 CHC patients who were classified into group 1 (1996-2001) and group 2 (2011-2016), the authors reported an increase in the patient age, higher rate of comorbidities, more advanced stage at the time of diagnosis, and a higher rate of HCC between 2 periods, from 1996-2001 to 2011-2016.[12]

Although the inconsistency among these studies seems to be in accordance with well-known regional variability in HCC epidemiology and staging, it should be noted that the findings reported in this multicenter study may reflect a more generalized view on HCC patients in Turkey, given that patients were recruited from all geographical regions across Turkey.

Accordingly, our findings support the global clinical epidemiology data on HCC, indicating HCC to show a strong male predilection (male-to-female ratio ranging from 2 : 1 to 7 : 1) and to affect individuals aged 50-70 years while an earlier onset (25-40 years) is also considered likely in hepatitis B endemic areas.[13,14]

The rates for NAFLD (4.1%) and cryptogenic liver disease (8.2%) in our cohort seem notable given the reported range (2.4% to 12.8%) of NASH-induced cirrhosis in HCC patients,[15] as well as the likelihood of identifying histological or clinical features of NAFLD in at least half of the patients commonly labeled as cryptogenic cirrhosis after further investigation.[16,17] Indeed, diabetic and overweight individuals are suggested as being likely to develop NAFLD and NASH that may result in cryptogenic cirrhosis and NASH-induced HCC.[18]

Notably, Turkey is considered among the countries with the highest NAFLD prevalence (>30%) in line with high obesity prevalence (32.1%).[19,20] Hence, along with the data on prevalence of diabetes (22.9%) and overweight/obesity (53.3%) in our cohort, our findings seem to support the growing contribution of the metabolic risk factors commonly related to NAFLD or NASH in HCC etiology.[5,7] This is important, given that progression to cirrhosis in NAFLD patients reduces the likelihood of detecting steatohepatitis in imaging or biopsy (burned-out NASH), while NASH itself induces progression to cirrhosis or HCC in other etiologies such as alcoholic liver diseases. Hence, lifestyle modification including prevention of obesity and control of metabolic diseases (i.e., diabetes and NAFLD) seems to be important in reducing the risk of HCC, in addition to other measures such as universal HBV vaccination, identification of the at-risk population by mass screening of the general population, implementation of HCC surveillance among the at-risk population, and antiviral therapy.[17,21]

Although smoking was reported to be associated with increased relative risk (RR, 1.51) for HCC in a meta-analysis of 38 cohort and 58 case control studies,[22] it does not seem possible to consider smoking as a definite risk factor for HCC based on our findings, since the percentage of active smokers achieved in the current study was similar to the average rate of overall active smokers (26.5%) in Turkey.[23] Our findings are in line with lower contribution of alcoholic etiology (range, 6% to 14%) to global incident cases of HCC in countries where viral hepatitis is the leading cause of HCC.[24] Nonetheless, given that 19.0% of our patients reported cessation of alcohol, it should be noted that while alcohol cessation is associated with a 6-7% reduction in the risk of HCC per year, the detrimental effects of alcohol are considered to remain for decades, with a wash-out period of 23 years estimated to be necessary to reach the same incidence of HCC with abstinent patients.[25]

In our cohort, family history for HCC was evident in 6.3% of patients (first-degree relatives in 72.4%). This finding is important given that family history of HCC has been suggested to increase the risk of HCC in patients with viral hepatitis, particularly when accompanied by HBV/HCV infection.[26] A need for a more intensive management of HBV infection and HCC surveillance has been emphasized in patients with a family history of HCC, given that family history of HCC multiplies the risk of HCC at each stage of HBV infection.[27] Notably, positive family history for hepatitis was evident in 27.9% and 10.9% of HBV and HCV patients in our study, along with a 6.3% rate of family history for HCC.

Although the role of AFP in screening and diagnosis remains controversial, it has prognostic significance. Increase in AFP levels is observed only in 10-20% of early stage HCC patients.[28] Nonetheless, it should be noted that an improvement in accuracy of AFP is expected as HCC epidemiology shifts from an HCV-predominant to a NASH-predominant etiology.[29] AFP levels at the time of HCC diagnosis in our cohort (401-1000 ng/dL in 9.9%, >1000 ng/dL in 22.3%) seem notable given AFP levels >400 ng/mL were reported to be an independent risk factor associated with an 8.9-fold increased risk for poor prognosis after liver transplantation for HCC patients in a past study from Turkey.[30] In addition, in a systematic

review of 13 studies, AFP >1000 ng/mL has been suggested to be associated with poorer outcomes from liver transplantation for HCC.[31]

Conventionally, HCC has been classified by the tumor-node-metastasis (TNM) staging without consideration of liver function.[9] In this regard, use of BCLC classification in HCC staging has strongly been recommended given that it links prognostic variables (tumor status, liver function, and health performance) with treatment strategy, such as consideration of curative intents in very early to early stage, loco-regional therapy in intermediate stage, first-line (sorafenib, lenvatinib) and second-line (regorafenib, cabozantinib) systemic therapy in advanced stage, and best supportive care in terminal stage disease.[32] Accordingly, our findings revealed a considerable discordance between BCLC and TNM staging, with identification of BCLC stage C-D disease in 11.5% of TNM Stage I patients and in 41.2% of TNM Stage II patients, emphasizing the role of assessing the organ functions besides TNM system in staging for HCC. Hence, presence of advanced (BCLC C) stage HCC in 26.5% of patients at the time of diagnosis in our cohort indicates that treatment options are limited with supportive therapy in nearly one-third of our study population, while 43.1% were in early stages (BCLC 0 or A), allowing for curative treatment.

A documented liver disease, the presence of known cirrhosis, and receipt of gastroenterology care were considered as the 3 strongest predictors for increased likelihood of receiving HCC screening.[33] In this regard, it should be noted that 49.8% of our patients were under follow-up with former diagnosis of cirrhosis or hepatitis, while HCC was the first diagnosis in 50.2% of patients Moreover, referral patients directly diagnosed with HCC had larger tumor size and more advanced BCLC stage when compared to patients with prior diagnosis of cirrhosis or hepatitis. This seems to support the likelihood of insufficient awareness of HCC risk factors and poor adherence to screening practices for cirrhotic patients in the primary care practice.[34] Similarly, in a past study from Turkey among newly diagnosed HCC patients, only 31.4% of patients were reported to be on a regular follow-up with a combined use of scheduled liver ultrasonography and AFP measurement at the time of diagnosis.[11] The authors also noted that patients who had regular follow-up and screening with AFP-ultrasonography were diagnosed at an earlier BCLC stage (stage 0-A; 57% vs.32%).[23] Notably, in a past study on comparison of imaging and pathology interpretation, diagnosis, and management plan between the outside provider and the multidisciplinary liver clinic (MDLC) for 343 patients with liver tumors, the authors reported that outside providers referred 53% of patients and the rest were self-referred.[35] They also noted that the referral to the MDLC resulted in alterations in the interpretation of imaging (18%) and of biopsy (10%), a change of diagnosis (8%), alterations of management plan (42%) and tumor resectability (5%), emphasizing the significant impact of patient assessment by MDLC on management, resulting in alterations to imaging and pathology interpretation, diagnosis, and management plan.[35]

The AASLD recommends surveillance of adults with cirrhosis, using US with/or without AFP every 6 months, while the use of either multiphasic CT or multiphasic MRI is recommended for diagnostic evaluation of HCC rather than as the primary modality for the surveillance. The guidelines also recommend against routine biopsy of indeterminate nodule and screening of patients with Child–Pugh class C cirrhosis unless they are on the transplant waiting list.[36]

Accordingly, our findings emphasize the role of an increased awareness among the physicians regarding the utility and role of routine screening and surveillance for patients with HCV and cirrhosis to increase chance for curative therapy via early tumor detection.[6,7,29,33,34]

Certain limitations to this study should be considered. First, due to the observational nature, non-randomized allocation, and thereby the likelihood of main selection bias and confounding is possible. Second, although providing data on real-life clinical practice via multicenter design at 25 centers representing all geographical regions across Turkey, potential lack of generalizability seems another important limitation of the current study due to relatively small sample size and inclusion of only tertiary care gastroenterology and oncology clinics. Third, fewer patients than initially estimated via sample size calculation could be included in the study, since only 547 patients complied with the inclusion/exclusion criteria. Nevertheless, despite these certain limitations, given the restricted amount of national data available on characteristics of newly diagnosed HCC patients in Turkey, our findings represent a valuable contribution to the literature.

In conclusion, our findings in a cohort of newly diagnosed HCC patients across Turkey revealed HBV infection as the leading etiology along with the presence of moderate-to-advanced disease in more than half of the patients at the time of diagnosis. However, 38% of patients had AFP

levels <20 ng/mL and 43.1% had BCLC stage 0-A disease at the time of diagnosis. In half of the patients, HCC was directly diagnosed at the time of referral, while the diagnosis followed previous cirrhosis or hepatitis in the other half of the patients. The referral patients directly diagnosed with HCC had larger tumor size and more advanced BCLC stage when compared to patients with prior diagnosis of cirrhosis or hepatitis. Hence, our findings emphasize a need for increased awareness among clinicians for HCC risk factors and utility of HCC screening among high-risk patients with hepatitis or cirrhosis to enable early disease detection and implementation of potentially curative treatment. The findings obtained from this study can be used to improve the public awareness on HCC and its etiology, and for the development of diagnostic and treatment policies for HCC patients at the national level. Implementation of screening programs for patients with high risk of HCC and controlling HBV and HCV infections at population level will decrease the incidence of HCC, enable early diagnosis and treatment, and increase overall survival of patients.

Ethics Committee Approval: The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and approved by the Ege University Faculty of Medicine Clinical Research Ethics Committee (Date of Approval: November 11, 2011; Reference number/Protocol No: 11-10/51).

Informed Consent: Written informed consent was obtained from each patient following a detailed explanation of the study objectives and protocol.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – U.S.A., O.S., C.A.; Design – U.S.A., O.S., C.A.; Supervision – U.S.A., O.S., C.A.; B.U., I.Y., D.D., S.O., M.A; Resource – U.S.A., Z.M.C.; Materials – U.S.A., Z.M.C.; Data Collection and/or Processing – U.S.A., B.U., O.S., K.Y., M.A., C.G., F.G., S.O., A.S., D.D., S.B.T., I.Y., H.A., C.A., R.I., O.O., A.B.; Analysis and/or Interpretation – A.B., U.S.A., Z.M.C; Literature Search – U.S.A., B.U., O.S., K.Y., M.A., C.G., F.G., S.O., A.S., D.D., S.B.T., I.Y., H.A., C.A., R.I., O.O.; Writing – U.S.A., O.S., C.A.; Critical Reviews – U.S.A., O.S., C.A.

Conflict of Interest: Zeynep Merve Cevik, is a Bayer Türk employee. Other authors declare that they have no conflict of interest.

Financial Disclosure: This study was supported by Bayer Turk. We thank Cagla Ayhan, MD and Sule Oktay, MD, PhD, from KAPPA Consultancy Training Research Ltd., Istanbul, who provided editorial support funded by Bayer Turk.

3K Registry Study Group (in descending order by the number of patients enrolled):

1. Ege University Faculty of Medicine, Izmir – Prof. Ulus Salih Akarca, MD
2. Izmir Ataturk Training and Research Hospital, Izmir – Prof. Belkis Unsal, MD
3. Mersin University Faculty of Medicine, Mersin – Prof. Orhan Sezgin, MD
4. Dicle University Faculty of Medicine, Diyarbakir – Prof. Kendal Yalcin, MD
5. Yuksek Ihtisas Training and Research Hospital, Ankara – Prof. Meral Akdogan
6. Haydarpasa Numune Training and Research Hospital, Istanbul – Assoc. Prof. Can Gonen, MD
7. Marmara University Faculty of Medicine, Istanbul – Assoc. Prof. Feyza Gunduz, MD
8. Gazi University Faculty of Medicine, Ankara – Prof. Seren Ozenirler,
9. Istanbul University Cerrahpasa Faculty of Medicine, Istanbul – Prof. Abdullah Sonsuz, MD
10. Akdeniz University Faculty of Medicine, Antalya – Prof. Dinc Dincer, MD
11. Ataturk University Faculty of Medicine, Erzurum – Prof. Salim Basol Tekin, MD
12. Ondokuz Mayis University Faculty of Medicine, Samsun – Prof. Idris Yucel, MD
13. Ankara University Faculty of Medicine, Ankara – Prof. Hakan Akbulut, MD
14. Sisli Etfal Training and Research Hospital, Istanbul – Assoc. Prof. Canan Alkım, MD
15. Ankara University Faculty of Medicine, Ankara – Prof. Ramazan Idilman, MD
16. Adana Baskent University Faculty of Medicine, Adana – Prof. Ozgur Ozyilkan, MD
17. Akdeniz University Faculty of Medicine, Antalya – Prof. Senol Coskun, MD
18. Inonu University Faculty of Medicine, Malatya – Prof. Murat Aladag, MD
19. Ankara Baskent University Faculty of Medicine, Ankara – Prof. Omer Dizdar, MD
20. Inonu University Faculty of Medicine, Malatya – Prof. Hakan Harputluoglu, MD
21. Dokuz Eylul University Faculty of Medicine, Izmir – Prof Omer Topalak, MD
22. Istanbul University Istanbul Faculty of Medicine, Istanbul – Prof. Faruk Aykan, MD
23. Haydarpasa Numune Training and Research Hospital, Istanbul – Burcak Erkol Yilmaz, MD
24. Haseki Training and Research Hospital, Istanbul – Mustafa Bozkurt, MD
25. Istanbul Medipol Hospital, Istanbul – Assoc. Prof. Ozcan Yildiz

REFERENCES

1. World Health Organization, International Agency for Research on Cancer. Global Cancer Observatory (GCO). Available at: http://globocan.iarc.fr/old/FactSheets/cancers/liver-new.asp. Accessed January 01, 2021.

2. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE–5-a population-based study. Lancet Oncol. 2014;15(1):23-34. [CrossRef]

3. Goutté N, Sogni P, Bendersky N, et al. Geographical variations in incidence, management and survival of hepatocellular carcinoma in a Western country. J Hepatol. 2017;66(3):537-544. [CrossRef].

4. Bertuccio P, Turati F, Carioli G, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol. 2017;67(2):302-309. [CrossRef].
5. Agosti P, Sabbà C, Mazzocca A. Emerging metabolic risk factors in hepatocellular carcinoma and their influence on the liver microenvironment. Biochim Biophys Acta Mol Basis Dis. 2018;1864(2):607-617. [CrossRef]
6. Fujiwara N, Friedman SL, Goossens N, Hoshida Y. Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol. 2018;68(3):526-549. [CrossRef]
7. Armengol C, Sarrias MR, Sala M. Hepatocellular carcinoma: present and future. Med Clin (Barc). 2018;150(10):390-397. [CrossRef]
8. Turkish Ministry of Health General Directorate of Public Health. Turkey Cancer Statistics 2016. Ankara, 2019. Avaliable at: https://hsgm.saglik.gov.tr/tr/kanser-istatistikleri. Accessed March 15, 2020.
9. Krishan S, Dhiman RK, Kalra N, et al. Joint consensus statement of the Indian National Association for study of the liver and Indian Radiological and Imaging Association for the diagnosis and imaging of hepatocellular carcinoma incorporating liver imaging reporting and data system. J Clin Exp Hepatol. 2019;9(5):625-651. [CrossRef]
10. Alacacioglu A, Somali I, Simsek I, et al. Epidemiology and survival of hepatocellular carcinoma in Turkey: outcome of multicenter study. Jpn J Clin Oncol. 2008;38(10):683-688. [CrossRef]
11. Ekinci O, Baran B, Ormeci AC, et al. Current state and clinical outcome in Turkish patients with hepatocellular carcinoma. World J Hepatol. 2018;10(1):51-61. [CrossRef]
12. Iliaz R, Yuce T, Torun S, et al. Changing epidemiology of chronic hepatitis C: patients are older and at a more advanced stage at the time of diagnosis. Eur J Gastroenterol Hepatol. 2019;31(10):1247-1249. [CrossRef]
13. Trad D, Bibani N, Sabbah M, et al. Known, new and emerging risk factors of hepatocellular carcinoma (review). Presse Med. 2017;46(11):1000-1007. [CrossRef]
14. Liu L, Li L, Zhou S, et al. Familial correlations of onset age of hepatocellular carcinoma: a population-based case-control family study. PLOS ONE. 2014;9(9):e108391. [CrossRef]
15. White DL, Kanwal F, El-Serag HB. Association between nonalcoholic fatty liver disease and risk for hepatocellular cancer, based on systematic review. Clin Gastroenterol Hepatol. 2012;10(12):1342-1359.e2. [CrossRef]
16. Duseja A, Sharma B, Kumar A, et al. Nonalcoholic fatty liver in a developing country is responsible for significant liver disease. Hepatology. 2010;52(6):2248-2249. [CrossRef]
17. Kumar A, Acharya SK, Singh SP, et al. 2019 Update of Indian National Association for Study of the Liver Consensus on Prevention, Diagnosis, and Management of Hepatocellular Carcinoma in India: The Puri II Recommendations. J Clin Exp Hepatol. 2020;10(1):43-80. [CrossRef]
18. Marrero JA, Fontana RJ, Su GL, et al. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology. 2002;36(6):1349-1354. [CrossRef]
19. World Health Organization. Obesity and overweight 2016. Available at: http://www.who.int/gho/ncd/risk_factors/overweight_obesity/obesity_adults/en/. Accessed March 15, 2020.
20. Kaya E, Yılmaz Y. Non-alcoholic fatty liver disease: A growing public health problem in Turkey. Turk J Gastroenterol. 2019;30(10):865-871. [CrossRef]
21. Zanetti AR, Van Damme P, Shouval D. The global impact of vaccination against hepatitis B: a historical overview. Vaccine. 2008;26(49):6266-6273. [CrossRef]
22. Lee YC, Cohet C, Yang YC, et al. Meta-analysis of epidemiologic studies on cigarette smoking and liver cancer. Int J Epidemiol. 2009;38(6):1497-1511. [CrossRef]
23. Turkish Thoracic Society. Turkish Thoracic Society 19th Annual Congress Tobacco Control Study Group Declaration; 2016. Available at: https://www.toraks.org.tr/News.aspx?detail=3067. Accessed March 15, 2020.
24. Ganne-Carrié N, Nahon P. Hepatocellular carcinoma in the setting of alcohol-related liver disease. J Hepatol. 2019;70(2):284-293. [CrossRef]
25. Heckley GA, Jarl J, Asamoah BO, G-Gerdtham U. How the risk of liver cancer changes after alcohol cessation: a review and meta-analysis of the current literature. BMC Cancer. 2011;11:446. [CrossRef]
26. Turati F, Edefonti V, Talamini R, et al. Family history of liver cancer and hepatocellular carcinoma. Hepatology. 2012;55(5):1416-1425. [CrossRef]
27. Loomba R, Liu J, Yang HI, et al. Synergistic effects of family history of hepatocellular carcinoma and hepatitis B virus infection on risk for incident hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2013;11(12):1636-45.e1. [CrossRef]
28. Yamashita T, Forgues M, Wang W, et al. EpCAM and alpha-fetoprotein expression defines novel prognostic subtypes of hepatocellular carcinoma. Cancer Res. 2008;68(5):1451-1461. [CrossRef]
29. Frenette CT, Isaacson AJ, Bargellini I, Saab S, Singal AG. A practical guideline for hepatocellular carcinoma screening in patients at risk. Mayo Clin Proc Innov Qual Outcomes. 2019;3(3):302-310. [CrossRef]
30. Yaprak O, Akyildiz M, Dayangac M, et al. AFP level and histologic differentiation predict the survival of patients with liver transplantation for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int. 2012;11(3):256-261. [CrossRef]
31. Hakeem AR, Young RS, Marangoni G, Lodge JPA, Prasad KR. Systematic review: the prognostic role of alpha-fetoprotein following liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther. 2012;35(9):987-999. [CrossRef]
32. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236. [CrossRef]
33. Choi DT, Kum HC, Park S, et al. Hepatocellular carcinoma screening is associated With increased survival of patients With cirrhosis. Clin Gastroenterol Hepatol. 2019;17(5):976-987.e4. [CrossRef]
34. Kumar A. Current practices in management of hepatocellular carcinoma in India: results of an online survey. J Clin Exp Hepatol. 2014;4(Suppl 3):S140-S146. [CrossRef]
35. Zhang J, Mavros MN, Cosgrove D, et al. Impact of a single-day multidisciplinary clinic on the management of patients with liver tumours. Curr Oncol. 2013;20(2):e123-e131. [CrossRef]
36. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018;68(2):723-750. [CrossRef]