Research Article

HEPATOLOGY FORUM

Characteristics of patients with hepatocellular carcinoma

doi: 10.14744/hf.2022.2022.0028

Characteristics of patients with hepatocellular carcinoma: A multicenter study

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Abstract

Background and Aim: The aim of the present study was to examine the etiology of hepatocellular carcinoma (HCC) by underlying cause and determine the characteristics and clinical features of patients with HCC.

Materials and Methods: The study comprised 1802 HCC patients diagnosed and followed up by Liver Diseases Outpatient Clinics in 14 tertiary centers in Turkey between 2001 and 2020.

Results: The mean age was 62.3±10.7 years, and 78% of them were males. Of the patients, 82% had cirrhosis. Hepatitis B virus (HBV) infection was the most common etiology (54%), followed by hepatitis C virus (HCV) infection (19%) and nonalcoholic fatty liver disease (NAFLD) (10%). Of the patients, 56% had a single lesion. Macrovascular invasion and extrahepatic spread were present in 15% and 12% of the patients, respectively. The median serum alpha-fetoprotein level was 25.4 ng/mL. In total, 39% of the patients fulfilled the Milan Criteria. When we compared the characteristics of patients diagnosed before and after January 2016, the proportion of NAFLD-related HCC cases increased after 2016, from 6.6% to 13.4%.

Conclusion: Chronic HBV and HCV infections remain the main causes of HCC in Turkey. The importance of NAFLD as a cause of HCC is increasing.

Keywords: Clinical characteristics; etiology; hepatocellular carcinoma.

How to cite this article: Guzelbulut F, Karaogullarindan U, Akkiz H, Altintas E, Demirtas CO, Bahadir O, et al. Characteristics of patients with hepatocellular carcinoma: A multicenter study. Hepatology Forum 2022; 3(3):71–76.

Received: August 03, 2022; **Accepted:** August 15, 2022; **Available online:** September 23, 2022

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Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Cirrhosis and hepatocellular carcinoma (HCC) are major health problems worldwide. HCC is the sixth most common cancer and the third most common cause of cancer-related mortality worldwide.[1] Cirrhosis is a risk factor for developing HCC and is present in 70%–90% of all HCC patients.[2,3] The etiologies of cirrhosis and HCC vary.[2,3] Hepatitis C virus (HCV) infection and alcohol consumption are the most common risk factors for cirrhosis and HCC in Western countries, whereas hepatitis B virus (HBV) infection is the leading cause of cirrhosis and HCC in East Asia and Africa.[2–4] Although HBV and HCV infections and alcohol consumption are the causes of HCC in approximately 80%–90% of cases,[5] nonalcoholic fatty liver disease (NAFLD) is becoming one of the most common causes of cirrhosis and HCC.[6]

In Turkey, HBV and HCV infections remain major causes of liver-related morbidity and mortality and the most common causes of cirrhosis and HCC in more than 50% of HCC cases.[7–15] The data regarding the etiologic and clinical characteristics of HCC in a large cohort of Turkish patients are limited. The aim of the present study was to examine the etiology of HCC by underlying cause and to determine the characteristics and clinical features of patients with HCC in Turkey.

Materials and Methods

This was a multicenter, retrospective cohort study comprising patients diagnosed with HCC who were followed up in the Liver Disease Outpatient Clinics of 14 tertiary centers in Turkey between 2001 and 2020. Among the centers, 9 had liver transplantation units. For data collection and recording, a specific electronic case report form (CRF) was designed. Each center entered the relevant data in the CRF. This study was approved by the local Ethical Committee (approval number: 09.2020.722, approval date: July 24, 2020).

Cirrhosis was defined based on clinical, biochemical, and histological findings when available. ICD-10 codes were used to identify cirrhosis

Table 1. Baseline characteristics of all HCC patients

Age, years, mean±SD	62.3±10.7
Gender, male, n (%)	1403 (78.0)
BMI, kg/m^2, median (IQR)	27.7 (6.8)
Obesity (BMI ≥30) (%)	32.7
Alcohol history (%)	21.1
Smoking history (%)	55.2
Diabetes mellitus (%)	29.9
Hypertension (%)	35.5
Hyperlipidemia (%)	62.5
Cirrhosis, n (%)	1468 (81.5)
Child-Pugh class A, n (%)	697 (47.5)
Child-Pugh class B, n (%)	523 (35.6)
Child-Pugh class C, n (%)	248 (16.9)
MELD score, mean±SD	11.4±5.1
Etiology, n (%)	
Viral hepatitis	1380 (76.6)
HBV	981 (54.4)
HCV	339 (18.8)
HDV	50 (2.8)
HBV–HCV coinfection	10 (0.6)
NAFLD	179 (9.9)
Cryptogenic	154 (8.6)
Alcohol-related liver disease	64 (3.6)
Autoimmune liver diseases	16 (0.9)
Miscellaneous	9 (0.5)

BMI: Body mass index; SD: Standard deviation; MELD: Model for end-stage liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Chronic delta virus.

Table 2. Tumor characteristics of HCC patients

Number of lesions, n (%)	
Single lesion	1016 (56.4)
Multinodular	786 (43.6)
Largest tumor diameter, n (%)	
≤30 mm	586 (32.6)
>30 mm	1212 (67.4)
Macrovascular invasion, n (%)	276 (15.3)
Extrahepatic spread, n (%)	217 (12.0)
BCLC classification, n (%)	
Stage 0	170 (9.4)
Stage A	697 (38.7)
Stage B	248 (13.8)
Stage C	253 (14.0)
Stage D	434 (24.1)
Milan criteria, n (%)	38.8
AFP, ng/mL, median (IQR)	25.4 (405.2)
AFP, n (%)	
Normal (<9 ng/mL)	586 (34.4)
9 to <200 ng/mL	608 (35.7)
≥200 ng/mL	511 (30.0)

AFP: Alpha-fetoprotein.

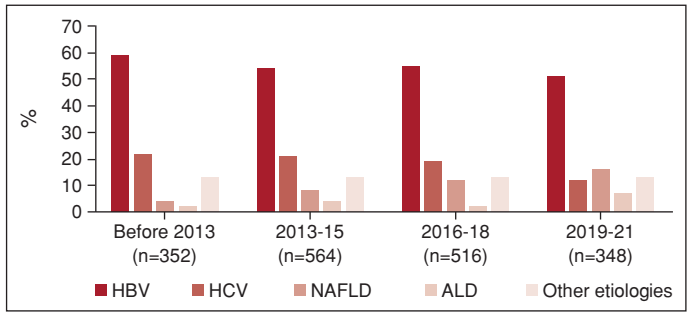

Figure 1. HCC etiologies over the years.

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; NAFLD: Nonalcoholic fatty liver disease; ALD: Alcoholic liver disease.

and its complications. Based on ICD-10 diagnostic codes, the patients were categorized as having chronic HBV infection, chronic HCV infection, chronic delta virus (HDV) infection, NAFLD, cryptogenic cirrhosis, alcohol-related liver disease (ALD), autoimmune liver diseases (autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis), metabolic liver diseases (Wilson's disease, hemochromatosis, and alpha-1 antitrypsin deficiency), and vascular liver disease (Budd-Chiari Syndrome).

HCC was diagnosed based on clinical, biochemical, radiological [dynamic magnetic resonance imaging (MRI) and/or triphasic computed tomography (CT)] and histological findings when available.[2] HCC was staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system.[16] The etiological diagnosis was made based on international criteria. Child-Pugh's and Model for End-Stage Liver Disease (MELD) scores were used for assessing the severity of chronic liver disease (CLD) and were calculated during admission and follow-up visits.

Laboratory investigations included serum alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, prothrombin time, and alpha-fetoprotein (AFP). Complete blood cell counts were obtained by the local central laboratory of each unit.

Definitions: The primary endpoints of the study were to determine the etiology of HCC in this patient population and to define the clinical characteristics of the patients. The secondary endpoints were to determine trends in the etiology of HCC by underlying cause before January 2016 and after January 2016.

HCC lesions were defined according to number as solitary or multifocal. Lesion size was defined according to the size of the largest lesion (≤30 and >30 mm. Macrovascular (portal vein and/or hepatic vein) invasion and extrahepatic spread were recorded when present.

Follow-Up: Patients were seen at regular intervals in an outpatient clinic during the follow-up period. Further investigations included surveillance for HCC with ultrasonographic examination or cross-sectional imaging, and AFP measurements were made every 6 months. If necessary, dynamic CT or MRI was performed.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and percent were used for descriptive statistics. Categorical variables

Table 3. Comparison of HCC patients based on the association of HBV, HCV, and NAFLD

	HBV (n=981)	HCV (n=339)	NAFLD (n=179)	p
Age, years, mean±SD	60.7±10.0	67.0±8.8	65.8±10.0	**0.0001**[1]
Gender, male, n (%)	831 (84.9)	213 (63.0)	122 (68.2)	**0.0001**[2]
BMI, kg/m^2, median (range)	27.1 (16.8–45.9)	27.3 (18.6–40.8)	32 (21.2–44.2)	**0.0001**[3]
Obesity (BMI ≥30) (%)	28.1	32.6	63.0	**0.0001**[4]
Alcohol history (%)	19.4	11.5	12.6	**0.023**[5]
Smoking history (%)	59.1	38.7	52.9	**0.0001**[6]
Diabetes mellitus (%)	24.7	33.2	77.5	**0.0001**[7]
Hypertension (%)	30.7	42.9	61.6	**0.0001**[8]
Hyperlipidemia (%)	65.4	59.3	70.6	0.246
Cirrhosis, n (%)	785 (80.0)	285 (84.1)	152 (84.9)	0.116
MELD score, median (IQR)	10.0 (6.0)	10.0 (6.0)	9.0 (4.0)	0.154
Number of lesions, n (%)				**0.004**[9]
Single lesion	525 (53.5)	216 (63.7)	105 (58.7)	
Multinodular	456 (46.5)	123 (36.3)	74 (41.3)	
Largest tumor diameter, n (%)				0.186
≤30 mm	302 (30.8)	121 (35.8)	62 (34.8)	
>30 mm	678 (69.2)	217 (64.2)	116 (65.2)	
Macrovascular invasion, n (%)	164 (16.7)	44 (13.0)	22 (12.3)	0.124
Extrahepatic spread, n (%)	128 (13.0)	30 (8.8)	21(11.7)	0.124
BCLC, n (%)				0.076
Stage 0	79 (8.1)	43 (12.7)	19 (10.6)	
Stage A	363 (37.0)	142 (41.9)	73 (40.8)	
Stage B	141 (14.4)	38 (11.2)	21 (11.7)	
Stage C	147 (15.0)	37 (10.9)	25 (14.0)	
Stage D	251 (25.6)	79 (23.3)	41 (22.9)	
Milan criteria, n (%)	355 (36.2)	154 (45.4)	72 (40.2)	**0.010**[10]
AFP, ng/mL, median (IQR)	30.9 (471.1)	30.0 (216.9)	12.0 (340.3)	0.092
AFP, n (%)				**0.0001**
Normal (<9 ng/mL)	303 (32.4)	86 (26.8)	75 (44.4)	**0.0001**[11]
9 to <200 ng/mL	335 (35.9)	148 (46.1)	46 (27.2)	**0.0001**[12]
≥200 ng/mL	296 (31.7)	87 (27.1)	48 (28.4)	0.259

Comparison between subgroups: [1]HBV vs HCV, p=0.0001; HBV vs NAFLD, p=0.0001. [2]HBV vs HCV, p=0.0001; HBV vs NAFLD, p=0.0001. [3]HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001. [4]HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001. [5]HBV vs HCV, p=0.017. [6]HBV vs HCV, p=0.0001; HCV vs NAFLD, p=0.016. [7]HBV vs HCV, p=0.002; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001. [8]HBV vs HCV, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001. [9]HBV vs HCV, p=0.001. [10]HBV vs HCV, p=0.003. [11]HBV vs NAFLD, p=0.003; HCV vs NAFLD, p=0.0001. [12]HBV vs HCV, p=0.001; HBV vs NAFLD, p=0.030; HCV vs NAFLD, p=0.0001.

were assessed by a Chi-squared test. For comparisons between two groups, the Mann–Whitney U test was used for nonnormally distributed variables. A p-value of less than 0.05 was considered significant.

Results

A total of 1802 patients diagnosed with HCC were included in the analysis. The mean age was 62.3±10.7 years (median: 63.0 years, range: 18–96 years), and male gender was predominant (78.0%). The mean body mass index (BMI) was 28.3±5.4 kg/m^2 (median: 27.7 kg/m^2), and 32.7% of the patients were obese. In the study population, 29.9% of the patients had diabetes mellitus (DM), 35.5% had hypertension, 55.2% were active or ex-smokers, and 21.1% consumed alcohol. Most of the patients were diagnosed cirrhosis (81.5%), with 47.5% of the patients were classified as having Child-Pugh class A, 35.6% classified as having Child-Pugh class B, and 16.9% classified as having Child-Pugh class C. The mean MELD score was 11.4±5.1 (Table 1).

The majority of the patients had HBV-associated HCC (54.4%), followed by HCV-associated (18.8%), NAFLD-associated (9.9%), cryptogenic cirrhosis-associated (8.6%), and ALD-associated HCC (3.6%) (Table 1). Among the HCC cases, 56.4% of the patients had a single HCC lesion, and the remaining patients had multinodular HCC (43.6%). In terms of lesion size, it was ≤30 mm in 32.6% of patients and >30 mm in 67.4% of the patients. Macrovascular invasion and extrahepatic spread were found in 15.3% and 12.0% of the patients, respectively. According to the BCLC staging system, 9.4% of the patients had stage 0, 38.7% had stage A, 13.8% had stage B, 14.0% had stage C, and 24.1% had stage D. In the study population, 38.8% of the patients fulfilled the Milan criteria. The median serum AFP level was 25.4 ng/mL (interquartile range: 405.2 ng/mL). AFP levels were within the normal range in 34.4% of patients. In 35.7% of cases, they were between ≥9 and 200 ng/mL. In 30.0% of cases, AFP levels were ≥200 ng/mL (Table 2).

Table 4. Comparison of patients diagnosed with HCC before and after January 2016

	Before 2016 (n=919)	After 2016 (n=883)	p
Age, years, mean±SD	61.5±10.3	63.0±11.0	0.003
Gender, male, n (%)	724 (78.9)	679 (77.1)	0.358
Obesity (BMI ≥ 30) (%)	32.7	32.6	0.981
Alcohol history (%)	20.6	21.7	0.658
Smoking history (%)	57.5	52.6	0.109
Diabetes mellitus (%)	26.9	33.1	**0.004**
Hypertension (%)	34.9	36.3	0.534
Hyperlipidemia (%)	63.9	61.8	0.606
Etiology, n (%)			**0.0001**
Viral hepatitis	740 (80.5)	640 (72.5)	**0.0001**
HBV	512 (55.7)	469 (53.1)	0.268
HCV	197 (21.4)	142 (16.1)	**0.004**
HDV	27 (2.9)	23 (2.6)	0.667
Cryptogenic	81 (8.8)	73 (8.2)	0.696
NAFLD	61 (6.6)	118 (13.4)	**0.0001**
Cirrhosis, n (%)	768 (83.6)	700 (79.3)	**0.019**
Child-Pugh, n (%)			**0.0001**
Class A	326 (42.4)	371 (53.0)	**0.0001**
Class B	280 (36.5)	243 (34.7)	0.486
Class C	162 (21.1)	86 (12.3)	**0.0001**
MELD score (mean±SD)	11.8±5.2	11.0±4.9	**0.003**
Number of lesions, n (%)			0.625
Single lesion	513 (55.8)	503 (57.0)	
Multinodular	406 (44.2)	380 (43.0)	
Largest tumor diameter, n (%)			0.232
≤30 mm	287 (31.3)	299 (33.9)	
>30 mm	630 (68.7)	582 (66.1)	
Macrovascular invasion, n (%)	161 (17.5)	115 (13.0)	**0.008**
Extrahepatic spread, n (%)	85 (9.2)	132(14.9)	**0.0001**
BCLC, n (%)			0.170
Stage 0	91 (9.9)	79 (8.9)	
Stage A	336 (36.6)	361 (40.9)	
Stage B	126 (13.7)	122 (13.8)	
Stage C	125 (13.6)	128 (14.5)	
Stage D	241 (26.2)	193 (21.9)	
Milan criteria, n (%)	346 (37.6)	354 (40.1)	0.288
AFP, ng/mL, median (IQR)	33.0 (513.8)	17.0 (312.5)	**0.0001**
AFP, n (%)			**0.0001**
Normal (<9 ng/mL)	238 (27.4)	348 (41.6)	**0.0001**
9 to <200 ng/mL	351 (40.4)	257 (30.7)	**0.0001**
≥200 ng/mL	280 (32.2)	231 (27.6)	**0.0001**

HBV: Hepatitis B virus; HCV: Hepatitis C virus; HDV: Chronic delta virus; NAFLD: Nonalcoholic fatty liver disease; MELD: Model for End-Stage Liver Disease; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha-fetoprotein.

Patients with HBV-related HCC were younger and showed male predominance compared with those with HCV- and NAFLD-related HCC (both p<0.001). A single HCC lesion was more common among HCV-related HCC cases than HBV-related HCC cases (p=0.004). More HCV-related HCC patients (45.4%) than HBV-related HCC patients (36.2%) fulfilled the Milan criteria (p=0.003). NAFLD-related HCC patients had higher BMI and lower AFP levels than HBV- and HCV-related HCC patients (p<0.001) (Table 3).

When the characteristics of the patients diagnosed before and after January 2016 were compared, those diagnosed with HCC after January 2016 were older (p=0.003) and more commonly had DM (p=0.004) than those diagnosed before this date. The proportion of HCV-related HCC decreased from 21.4% to 16.1% after January 2016 (p=0.004), whereas the proportion of NAFLD-related HCC increased from 6.6% to 13.4% (p<0.001). The macrovascular invasion was detected more frequently among patients diagnosed with HCC prior to January 2016, and extrahepatic spread was detected more frequently after January 2016 (p=0.008 and p=0.0001, respectively). The proportion of HCC patients in each BCLC stage and the proportion that fulfilled the Milan criteria were similar before and after January 2016 (p=0.170 and p=0.288, respectively). More HCC patients had normal AFP levels after January 2016 (Table 4).

Discussion

This is the largest study yet to determined etiologic and clinical characteristics of HCC patients in Turkey. In the present study, chronic viral hepatitis remains the major risk factor contributing to the development of HCC. HBV infection was most commonly associated with HCC, followed by HCV infection and NAFLD. HCC patients with HBV infection were younger with male predominance, compared with those with HCV infection and NAFLD. These results are compatible with those of previous studies, which demonstrated that chronic viral hepatitis was the main cause of HCC.[7–14,17] These results indicate that chronic viral hepatitis remains the most common risk factor for the development of HCC in Turkey over the last two decades.

The etiologic trend of CLD, cirrhosis, and HCC has changed over time worldwide.[18–20] Global vaccination against HBV and the advent of potent antivirals against HBV and HCV infections have resulted in a decrease in the incidence of viral hepatitis-related cirrhosis and HCC.[18,20,21] On the other hand, the prevalence of NAFLD has increased steadily.[18] The increasing prevalence of obesity, DM, and metabolic syndromes exacerbates the risk of NAFLD-related cirrhosis and HCC.[6] According to the literature, NAFLD is the most common cause of CLD, cirrhosis, and HCC in the United States, with an increase of 170% in the number of patients with NAFLD on the liver transplantation waiting list.[22–24] Alcohol consumption continues to be one of the major contributors to CLD in the Western population.[25] In Turkey, from 2002 to 2013, the prevalence of obesity and DM increased by 40% and 90%, respectively, based on two cross-sectional, population-based surveys (Turkish Diabetes Epidemiology Study, TURDEP I and II).[26,27] In the second study (TURDEP II), the prevalence of obesity was 36%, and the prevalence of DM was 16.5%.[27] Yilmaz et al.[28] reported that the prevalence of metabolic syndrome was 35%, and the prevalence of NAFLD was 46%. Previous studies focused on the etiology of cirrhosis and HCC did not report the proportion of NAFLD-related cirrhosis cases with and without HCC.[7,11] However, some investigators recently documented that NAFLD was a risk factor for the development of HCC in 3.5%–5.6% of cases.[12,13] A recent study in Turkey reported that NAFLD was one of the most common causes of cirrhosis, accounting for 8.5% of cases.[15] In the present study, 33% of the HCC patients were obese, 30% had DM, and 36% had hypertension. NAFLD-related cir-

rhosis was one of the most frequent causes of HCC, accounting for 10% of cases. In this study, ALD accounted for 4% of the HCC cases. When we compared HCC cases according to etiology before and after January 2016, the proportions of HCC cases attributed to HBV decreased from 56% to 53%, and the proportion of HCC cases attributed to HCV decreased from 21% to 16%. According to our findings, chronic viral hepatitis-related HCC declined (from 81% to 73%) throughout the study period, whereas NAFLD-related HCC increased (from 6.6% to 13.4%).

The risk of HCC recurrence is related to tumoral characteristics, such as the lesion diameter and the number of nodules.[16] In the present study, 82% of the HCC patients had cirrhosis, of which half had decompensated cirrhosis. Etiology did not affect the severity of the disease. Of the patients, 56% had a single HCC nodule, with the remaining 44% having multinodular HCC. The macrovascular invasion was present in 15% of cases and extrahepatic disease in 12% of cases. Of the patients, 39% fulfilled the Milan Criteria. Before and after January 2016, there was no change in the detection rate of small HCC lesions (≤3 nodules). However, over time, early detection led to a decrease in the detection of macrovascular invasion (Fig. 1).

The distribution of what according to the BCLC staging was similar. Serum AFP levels and abdominal sonography are usually included in HCC surveillance programs. In the present study, after January 2016, the mean AFP levels decreased and the proportions of patients with normal or near normal AFP levels increased. This finding is compatible with that of previous studies, which found normal or near normal serum AFP levels in around 50% of HCC cases.[12,13] These results indicate that awareness of HCC has increased and that screening and surveillance of cirrhotic patients at risk for HCC have improved in recent years.

The present study was a multicenter, large, collaborative retrospective cohort study. This cohort has several limitations. First, the study included HCC patients from tertiary referral centers throughout Turkey. The patients attending these centers may not be representative of the Turkish population as a whole. Second, due to the retrospective design of this study, the data on the patients' characteristics, such as alcohol and smoking habits, comorbidities, and BMI, were not available for all patients.

In conclusion, based on data pertaining to the last two decades, HBV- and HCV-associated HCC remain common in Turkey. HCC patients were mostly cirrhotic and showed male predominance. HBV-associated HCC patients were younger than HCV- and NAFLD-related HCC cases. The proportion of NAFLD-related HCC has increased in the last two decades.

Ethics Committee Approval: This study was approved by the local Ethical Committee (approval number: 09.2020.722, approval date: July 24, 2020).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – FG, UK, HA, EA, COD, OB, CK, AEY, MG, HRB, PG, DTG, CS, IT, GC, VG, SY, GA, RAA, UA, MD, SV, HS, HLD, FD, MAK, HYB, HS, OCO, USA, ZK, FG, RI; Design – FG, UK, EA, COD, OB, CK, AEY, MG, HRB, PG, DTG, CS, IT, GC, VG, SY, GA, RAA, UA, MD, SV, HS, HLD, FD, MAK, HYB, HS, OCO, USA, ZK, FG, RI; Supervision – FG, UK, HA, EA, COD, OB, CK, AEY, MG, HRB, PG, DTG, CS, IT, GC, VG, SY, GA, RAA, UA, MD, SV, HS, HLD, FD, MAK, HYB, HS, OCO, USA, ZK, FG, RI; Data Collection and/or Processing – FG, UK, COD, OB, CK, AEY, MG, HRB, PG, DTG, CS, IT, GC, VG, SY, GA, RAA, UA, MD, SV, HS; Analysis and/or Interpretation – FG, RI; Literature Search – FG, HA, EA; Writing – FG; Critical Reviews – HA, EA, FD, MAK, HYB, HS, OCO, USA, ZK, FG, RI.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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