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.

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...
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. HCC was staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system. 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.

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 1. Baseline characteristics of all HCC patients |
| --- |
| **Age, years, mean±SD** | 62.3±10.7 |
| **Gender, male, n (%)** | 1403 (78.0) |
| **BMI, kg/m², 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) |
| **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) |

| HBV | HCV | NAFLD | ALD | Other etiologies |
| --- | --- | --- | --- | --- |
| Before 2013 | 2013-15 | 2016-18 | 2019-21 |
| HBV | HCV | NAFLD | ALD | Other etiologies |

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

Figure 1. HCC etiologies over the years.
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/m² (median: 27.7 kg/m²), 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 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 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<sup>1</sup> |
| Gender, male, n (%)| 831 (84.9)  | 213 (63.0)  | 122 (68.2)    | 0.0001<sup>2</sup> |
| BMI, kg/m², median (range) | 27.1 (16.8–45.9) | 27.3 (18.6–40.8) | 32 (21.2–44.2) | 0.0001<sup>3</sup> |
| Obesity (BMI ≥30) (%) | 28.1        | 32.6        | 63.0          | 0.0001<sup>4</sup> |
| Alcohol history (%) | 19.4        | 11.5        | 12.6          | 0.023<sup>5</sup> |
| Smoking history (%) | 59.1        | 38.7        | 52.9          | 0.0001<sup>6</sup> |
| Diabetes mellitus (%) | 24.7        | 33.2        | 77.5          | 0.0001<sup>7</sup> |
| Hypertension (%)    | 30.7        | 42.9        | 61.6          | 0.0001<sup>8</sup> |
| 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<sup>3</sup> |           |               |      |
| 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 (%) | 0.124 |           |               |      |
| Extrahepatic spread, n (%) | 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 (%) | 0.010       |            |               |      |
| Normal (<9 ng/mL)   | 355 (36.2)  | 154 (45.4)  | 72 (40.2)     |      |
| 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<sup>11</sup> |
| 9 to ≤200 ng/mL     | 335 (35.9)  | 148 (46.1)  | 46 (27.2)     | 0.0001<sup>12</sup> |
| ≥200 ng/mL          | 296 (31.7)  | 87 (27.1)   | 48 (28.4)     | 0.259 |

Comparison between subgroups: HBV vs HCV, p=0.0001; HBV vs NAFLD, p=0.0001; HBV vs HCV, p=0.0001; HBV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001; HBV vs NAFLD, p=0.0001; HCV vs NAFLD, p=0.0001.
In the present study, 33% of the HCC patients were HBV-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.[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.[13] In the present study, 33% of the HCC patients were obese, 30% had DM, and 36% had hypertension. NAFLD-related cir-

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).
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. 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. 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.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71(3):209-249.

2. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, 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.

3. 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.

4. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7(1):6.

5. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Ahera S, Ahmed M, Alam N, Alemayehu MA, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: Results from the global burden of disease study 2015. JAMA Oncol 2017;3(12):1683-1691.

6. Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. J Hepatol 2021;75(6):1476-1484.

7. Uzunalmıoğlu O, Yurdaydın C, Cetinkaya H, Bozkaya H, Sahin T, Coloydçoğlu S, et al. Risk factors for hepatocellular carcinoma in Turkey. Dig Dis Sci 2001;46(5):1022-1028.

8. Alacacioglu A, Somaaii I, Simsek I, Astarcioglu I, Ozkan M, Camci C, et al. Epidemiology and survival of hepatocellular carcinoma in Turkey: outcome of multicenter study. Jpn J Clin Oncol 2008;38(10):683-688.

9. Ekinci O, Baran B, Ormeci AC, Soyer OM, Gokturk S, Evrigen S, et al. Current state and clinical outcome in Turkish patients with hepatocellular carcinoma. World J Hepatol 2018;10(1):51-61.

10. Can A, Dogan E, Bayoglu IV, Tatli AM, Besiroglu M, Kocer M, et al. Multicenter epidemiologic study on hepatocellular carcinoma in Turkey. Asian Pac J Cancer Prev 2014;15(6):2923-2927.

11. Akkiz H, Carr BI, Yalçın KK, Guerra V, Kuran S, Altintas E, et al. Characteristics of hepatocellular carcinoma aggressiveness factors in Turkish patients. Oncology. 2018;94(2):116-124.

12. Akarca US, Uzunalimoğlu O, Yalçın K, Akdogan M, Gonen C, et al. Study Group OBOKR. Characteristics of Newly Diagnosed Hepatocellular Carcinoma Patients Across Turkey: Prospective Multicenter Observational 3K Registry Study. Turk J Gastroenterol 2021;32(12):1019-1028.

13. Vatansever S, Pakoz ZB. Trends of etiology and treatment in hepatocellular carcinoma over the years. Int J Res Med Sci. 2018;6(12):3895-3900.

14. Aslanov S, Gulsen Unal N, Senkaya A, Celik F, Murat Buyruk A, Uysal A, et al. Baseline characteristics associated with survival in patients with hepatocellular carcinoma. Hepatol Forum 2021;3(1):3-10.

15. Ildirim R, Aydogan M, Oruncu MB, Kartal A, Elhan AH, Elik Z, et al. Natural history of cirrhosis: changing trends in etiology over the years. Dig Dis 2021;39(4):358-365.

16. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendations: The 2022 update. J Hepatol 2022;76(3):681-693.

17. Zhao H, Zhu P, Han T, Ye Q, Xu C, Wu L, et al. Clinical characteristics analysis of 1180 patients with hepatocellular carcinoma secondary to hepatitis B, hepatitis C and alcoholic liver disease. J Clin Lab Anal 2020;34(2):e23075.

18. Younossi ZM, Stepanova M, Younossi Y, Golabi P, Mishra A, Rafiq N, et al. Natural history of cirrhosis: changing trends in etiology over the years. Dig Dis Sci 2001;46(5):1022-1028.

19. Younossi ZM, Stepnova M, Younossi Y, Golabi P, Mishra A, Rafiq N, et al. Natural history of cirrhosis: changing trends in etiology over the years. Dig Dis Sci 2001;46(5):1022-1028.

20. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73-84.

21. Puigvehi M, Hashim D, Haber PK, Dinani A, Schiano TD, Asgharpour A, et al. Current state and clinical outcome in Turkish patients with hepatocellular carcinoma. World J Hepatol 2018;10(1):51-61.
al. Liver transplant for hepatocellular carcinoma in the United States: Evolving trends over the last three decades. Am J Transplant 2020;20(1):220-230.
21. Belli LS, Perricone G, Adam R, Cortesi PA, Strazzabosco M, Facchetti R, et al; all the contributing centers (www.eltr.org) and the European Liver and Intestine Transplant Association (ELITA). Impact of DAAs on liver transplantation: Major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol 2018;69(4):810-817.
22. Kim D, Li AA, Perumpail BJ, Gadiparthi C, Kim W, Cholankeril G, et al. Changing trends in etiology-based and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019;69(3):1064-1074.
23. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70(1):151-171.
24. Wong RJ, Aguilar M, Cheung R, Perumpail RB, Harrison SA, Younossi ZM, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology 2015;148(3):547-555.
25. Han S, Yang Z, Zhang T, Ma J, Chandler K, Liangpunsakul S. Epidemiology of alcohol-associated liver disease. Clin Liver Dis 2021;25(3):483-492.
26. Satman I, Yilmaz T, Sengül A, Salman S, Salman F, Uygur S, et al. Population-based study of diabetes and risk characteristics in Turkey: results of the Turkish diabetes epidemiology study (TURDEP). Diabetes Care 2002 Sep;25(9):1551-1556.
27. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dincceg N, et al; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013;28(2):169-180.
28. Yilmaz Y, Yilmaz N, Ates F, Karakaya F, Gokcan H, Kaya E, et al; Turkish Association for the Study of the Liver (TASL); Fatty Liver Diseases Special Interest Groups. The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study. Hepatol Forum 2021;2(2):37-42.