Clinical and Epidemiological Characteristics of Hepatocellular Carcinoma Cases in East and Southeastern Region of Turkey: A Multicenter Retrospective Study

Türkiye'nin Doğu ve Güneydoğu Bölgesinde Hepatoselüler Karsinomalı Vakaların Klinik ve Epidemiyolojik Özellikleri: Çok Merkezli Retrospektif Çalışma

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ABSTRACT Objective: In this multicenter retrospective study, we aimed to investigate the epidemiological and clinical characteristics of patients with hepatocellular cancer (HCC) in the Eastern and Southeastern Anatolian regions of Turkey. **Material and Methods:** This study included 218 patients from 7 centers-Dicle University (n=96), Yüzüncü Yıl University (n=30), İnönü University (n=28), Fırat University (n=24), Gaziantep University (n=20), Atatürk University (n=19), and Harran University (n=1) hospitals. Information about patients was obtained through pre-prepared forms. Diagnosis of HCC was made histologically or with a combination of clinical, radiological, and laboratory findings. **Results:** The mean age of the patients was 57.67±12.03 with a male-to-female ratio of 5.8:1. Etiologically, 45% of the study group had HBV infection alone, 29% had HDV co-infection, 15% had HCV infection and 10% were idiopathic cases with unknown etiology. Cirrhotic background was present in 94% of the patients and 89% of cases had an advanced stage disease according to the Okuda classification. Alpha-fetoprotein levels were over 300 ng/ml in 81% of the patients. **Conclusion:** Hepatitis B virus infection followed by hepatitis delta virus infections appeared to be the leading etiological factors for HCC cases in our region. HBsAg carriage continues to be an important risk factor for HCC in Turkey. The fact that most of the HCC cases are in the late stages of disease, makes it necessary to use effective diagnosis and treatment methods with efficient screening and monitoring programs in our country.

Key Words: Carcinoma, hepatocellular; hepatitis B virus; hepatitis delta virus; epidemiology

ÖZET Amaç: Bu çok merkezli geriye dönük çalışmada, Türkiye'nin Doğu ve Güneydoğu Anadolu bölgesindeki hepatoselüler kanserli hastaların epidemiyolojik ve klinik özelliklerinin incelenmesi amaçlandı. **Gereç ve Yöntemler:** Çalışmaya 7 merkezden toplam 218 hasta alındı. Bu çalışmaya Dicle Üniversitesi (n=96), Yüzüncü Yıl Üniversitesi (n=30), İnönü Üniversitesi (n=28), Fırat Üniversitesi (n=24), Gaziantep Üniversitesi (n=20), Atatürk Üniversitesi (n=19), ve Harran Üniversitesi (n=1) Tıp Fakültesi Gastroenteroloji Bilim Dalları katıldı. Önceden belirlenmiş formlar kullanılarak her merkezden hastalar ile ilgili bilgiler istendi. Hepatoselüler kanser tanısı histolojik olarak veya klinik/radyolojik/laboratuar bulgulara dayanılarak konuldu. **Bulgular:** Hastaların yaş ortalaması 57,67±12,03 yıl, erkek/kadın oranı 5.8/1 idi. Hastaların %45'inde tek başına hepatit B virüsü enfeksiyonu, %29'unda hepatit delta virüsü koenfeksiyonu ve %15'inde hepatit C virüsü enfeksiyonu saptandı, %10'u da etiyolojisi bilinmeyen idiyopatik vakalardan oluşmaktaydı. Vakaların %94'ünde zeminde siroz bulunduğu, %89'unda ise Okuda sınıflamasına göre hastalığın ileri evrede olduğu tespit edildi. Alfa-feto protein düzeyi vakaların %81'inde 300 ng/ml'nin üzerinde idi. **Sonuç:** Bölgemizde hepatit B virüsü enfeksiyonu ve takiben hepatit delta virüsü enfeksiyonu, hepatoselüler kanserli vakalarda önde gelen etiyolojik faktörlerdir. HBsAg taşıyıcılığı Türkiye'de hepatoselüler kanser için önemli bir risk faktörü olmaya devam etmektedir. Hepatoselüler kanserli vakaların önemli bir kısmında hastalığın ileri evrede olması, bölgemizde etkin tarama ve izleme programları ile birlikte tanı ve tedavi yöntemlerinin de daha etkili bir şekilde kullanılması gerektiğini ortaya koymaktadır.

Anahtar Kelimeler: Karsinoma, karaciğer hücresi; hepatit B virüsü; hepatit delta virüs; epidemiyoloji

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Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and is increasing in incidence worldwide.[1-4] The incidence of HCC has doubled over the past thirty years in the United States.[5] This increase probably is due to an actual increase in incidence, the development of better diagnostic tools, screening and monitoring programs, enhanced referral patterns and the increased survival of cirrhotic patients.[6,7] The growing incidence of HCC is expected to reach a plateau around 2010-2015.[6]

The etiology varies somewhat geographically and hepatic cirrhosis is the underlying cause in most cases. HCC is common in the chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection and aflatoxin endemic areas. In Western societies, the relationship between HCC and hepatitis C virus is obvious[7], whereas association with hepatitis B is more evident in the developing countries.[8-11] The viral agents, especially HBV, have an important role in the HCC etiology in Asia, Middle East and Far East countries.[10,12] Each year more than 700000 new HCC cases are diagnosed worldwide.[8]

There are limited numbers of epidemiological studies on HCC disease in Turkey. Therefore, large-scale multi-center studies are needed in our country to investigate the epidemiological and clinical characteristics of HCC patients. This study aimed to determine the epidemiological, clinical, etiological, radiological, and histological characteristics of hepatocellular carcinoma with the cooperation of a large number of referral gastroenterology centers in the Eastern and Southeastern regions of Turkey.

MATERIAL AND METHODS

Two hundred and eighteen patients with HCC were included in this study from seven university hospitals in Turkey (96 patients from Dicle University in Diyarbakır, 30 patients from Yüzüncü Yıl University in Van, 28 patients from İnönü University in Malatya, 24 patients from Fırat University in Elazığ, 20 patients from Gaziantep University in Gaziantep, 19 patients from Atatürk University in Erzurum, and one patient from Harran University in Şanlıurfa). Retrospective patient data were obtained through pre-prepared forms between 2000 and 2004.

All patients with HCC were included in the study. The diagnosis of HCC was based on imaging techniques including ultrasound (USG), computerized tomography (CT), magnetic resonance imaging (MRI), alpha-feto protein (AFP) levels, and biopsy and/or histology from surgical specimens. The diagnostic criteria for HCC were either a confirmative histology or the presence of a space-occupying hepatic lesion with characteristic features on imaging studies together with an elevated AFP (>10 ng/mL). After 2001 the diagnosis of HCC was carried out according to internationally accepted criteria.[13]

Diagnosis of HBV infection was based on positive serology for HBsAg, HCV infection was based on positivity for anti-HCV antibodies, and hepatitis delta virus (HDV) infection on positivity for total anti-delta antibodies in serum. Hepatitis B viral markers were tested with enzyme immune assay (EIA), anti-HCV with second-generation EIA test, and total anti-delta with EIA. Alcohol abuse was considered significant when the reported intake was >50 g per day.

For all patients, demographic information, clinical features, histological type, mode of presentation at onset, the severity of background liver disease, etiology of liver disease, viral profiles, results of liver function tests, biochemical and hematological data were obtained. Assessment of hepatic function was calculated based on Child-Turcotte-Pugh (CTP) score.

The Okuda classification was used to assess tumor stage. Okuda stage of HCC was retrospectively analyzed based on data from medical records at the time of HCC diagnosis. The Okuda staging system used ascites, albumin and bilirubin levels as indicators of liver function and an estimate of the percentage of primary tumour involvement in the liver.[14] Ultrasonographic examination with CT or MRI confirmation, if needed was performed in all patients. Characteristics of the tumor on imaging

(types of tumor as uninodular, multinodular, or diffuse patterns) were assessed and the presence of extrahepatic metastases were recorded. All data, including staging of the tumour, were determined at the time of HCC diagnosis. The types of treatment received by patients were documented.

STATISTICAL ANALYSIS

Mean±standard deviation ($\bar{x} \pm SD$) values were calculated for continues variables and were given as descriptive statistics. Thus, the outcomes of current descriptive study were presented by using descriptive statistics. Therefore, all categorical variables were presented as number of patients, percentages and bar graphs. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) statistical package program was used to analyse the data.

RESULTS

PATIENT CHARACTERISTICS

A total of 218 patients with HCC were included in the study. The overall mean age at the time of HCC was 57.67±12.03. The mean age at admission was 55.73±10.68 years in Diyarbakır, 62.20±12.13 years in Van, 53.64±14.81 years in Malatya, 57.54±13.34 years in Gaziantep, 62.66±8.39 years in Elazığ, and 60.10±14.17 years in Erzurum (Table 1). One hundred and eighty-six patients (85%) were male and 32 patients (15%) were female, with a male-to-female ratio of 5.8:1 (Table 1).

BIOCHEMICAL PARAMETERS

The biochemical and hematological parameters of all patients were summarized in Table 2. The levels of aspartate transaminase (AST) (141.9±152.9 IU/L) and alanine transaminase (ALT) (96.41±92.32 IU/L) were elevated with an AST/ALT ratio of 1.5:1. Moreover, an increase in total bilirubin level and decrease in both albumin and hemoglobin levels were detected (Table 2).

TABLE 1: Age and sex distribution (n=218).

Variables	
Male/female, (Male %)	186/32, (85%)
Age (Year) (Mean±standard deviation)	57.67±12.03

TABLE 2: The biochemical and the hematological parameters of patients (n=218).

Parameters	Mean±standard deviation
ALT (IU/L)	96.41±92.32
AST (IU/L)	141.9±152.9
ALP (IU/L)	280.9±230.3
Total bilirubin (mg/dl)	3.59±5.10
Albumin (g/dl)	3.03±1.72
Platelet (K/UL)	217988±181846
Hemoglobin (g/dl)	11.82±2.19

ALT: Alanine aminotransferase; AST: Aspartam aminotransferase.

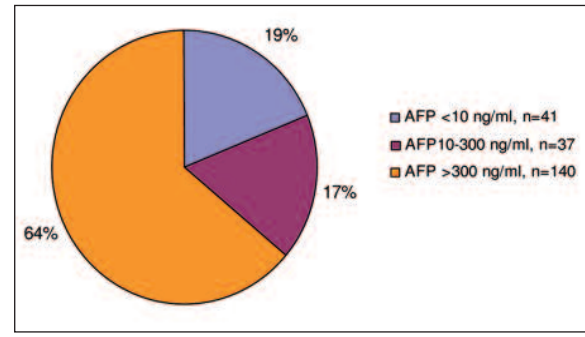

FIGURE 1: Percent distribution of AFP levels in patients.
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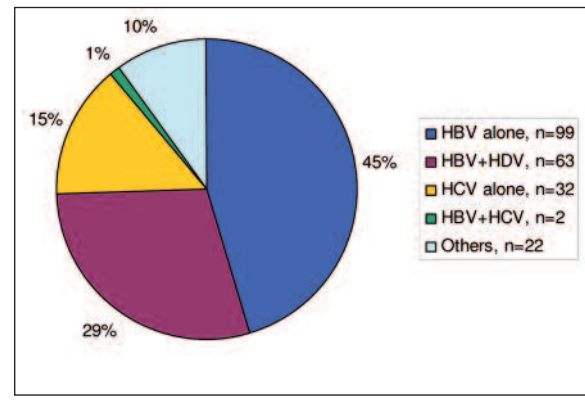

FIGURE 2: The etiological distribution of HCC patients (n=218).
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Percent distribution of AFP levels was summarized in Figure 1. The majority of patients had high levels of AFP in this cohort with only 43 patients (19%) with an AFP level of 20 ng/mL or less.

SEROLOGICAL FINDINGS

Etiological distribution of the patients was presented in Figure 2. The etiologic risk factors for HCC were hepatitis B alone (99 patients; 45%), hepatits B plus D (63 patients; 29%), and hepatitis C (32 pa-

tients; 15%) Two patients were co-infected with hepatitis B and hepatitis C. Twenty-two cases (10%) had other causes of HCC with no etiologic cause in the majority.

HBsAg was positive in 164 patients (75%), anti-HBs antibody in 9 (4%), HBeAg in 31 (14%), anti-HBe antibody in 136 (62%), anti-HBc IgG antibody in 169 (78%), total anti-delta antibody in 63 (29%) and anti-HCV antibody in 32 (15%). Anti-delta antibody positivity was up to 43% (41/96) in the center of Diyarbakır. The infection pattern was not similar among participating centers; namely, a large population of HCC was derived from hepatitis delta virus infection in Diyarbakır.

CLINICAL FEATURES AND CLINICAL STAGING

Clinical features and staging of the patients were presented in Figure 3. Figure 3 lists the number of patients in each disease and clinical staging groups. The majority of the patients had advanced stage liver disease. Eighty-four percent of patients had decompansated liver disease. The liver function, as reflected by the CTP score, was well preserved in only a minority of patients (n=22, 10%). The distribution of the 206 patients with cirrhosis was as follows: Child A, 22 (10%) patients; Child B, 87 (40%) patients; Child C, 97 (44%) patients. The majority of patients (89%) had advanced stage disease according to the Okuda classification of HCC.

TUMOR CHARACTERISTICS

Tumor characteristics as described by HCC background, the number of involved lobes, and involvement pattern were presented in Table 3. Cirrhotic background was present in 187 cases (94%), and only 12 cases (6%) had non-cirrhotic background. The tumor was located predominantly at the right lobe (56%). In 126 of 218 patients (58%) lesions were multinodular at presentation. Extrahepatic metastasis was present in 19% of patients. Half of the patients (51%) had no extrahepatic metastasis.

TABLE 3: Tumor characteristics of patients (n=218).

Variables	Number, (%)
Presence of cirrhosis	206, (94.49)
Non-cirrhotic background	12, (5.50)
Involvement of right lobe alone	122, (55.96)
Involvement of left lobe alone	26, (11.92)
Bilobular involvement	70, (32.11)
Uninodular	79, (36.23)
Multinodular	126, (57.79)
Diffuse involvement	13, (5.96)
Presence of extrahepatic metastasis	42, (19.26)
Absence of extrahepatic metastasis	110, (50.45)
Extrahepatic metastasis of undefined	66, (30.27)

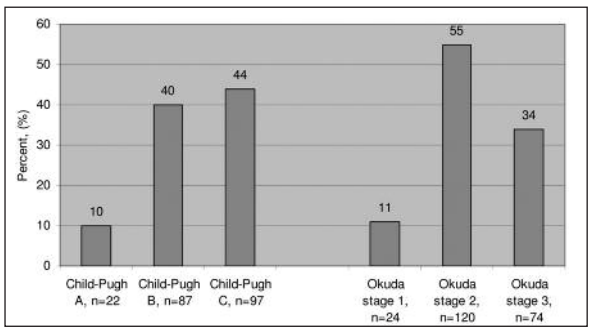

FIGURE 3: The clinical characteristics of patients (n=218).

HISTOLOGICAL FINDINGS

The diagnosis was made by liver biopsy in 33% of the patients (n=73). The type of histological distribution was presented in Table 4. Primary hepatocellular carcinoma was identified in the majority of cases (86%).

TREATMENT MODALITIES

The treatment modalities were presented in Figure 4. The treatment received by the patients included systemic chemotherapy (n=34, 16%), transcatheter arterial chemoembolization (TACE) (n=15, 7%), surgical resection (n=9, 4%), percutaneous ethanol injection (n=7, 3%), radiofrequency ablation (RFA) (n=2, 1%), liver transplantation (n=4, 2%), and supportive therapy (n=147, 67%). Most patients were treated by systemic chemotherapy and transarterial chemoembolization.

DISCUSSION

This is a comprehensive study of patients with HCC involving multiple centers in Turkey (seven major referral gastroenterology centers in the Eastern and Southeastern region of Turkey).

TABLE 4: Histological type of liver tumor proven by biopsy (n=73).

	Number (n, %)
Diagnosis made with biopsy	73/218, (33.48)
Diagnosis made without biopsy	145/218, (66.51)
Hepatocellular carcinoma	63/73 (86.30)
Fibrolamellar variant	3/73 (4.10)
Clear cell carcinoma	1/73 (1.36)
Mixed cholangiohepatocellular carcinoma	1/73 (1.36)
Undifferentiated	5/73 (6.84)

The features of HCC disease at presentation were collected from medical records of the patients. This study revelaed that male gender, age over 50 years and underlying advanced liver disease (cirrhosis) was associated with viral hepatitis B or D.

The demographics of the patients were consistent with previous epidemiological studies conducted in Turkey.[3,9] HCC is more common among men with an incidence rate two- or three-fold higher than among women.[5] In this study, males had a higher risk of HCC with a male to female ratio of 5.8. Almost all patients included in this study had a cirrhotic background (94%) and multinodular pattern was the dominant type of tumor in most cases (58%). These findings are in agreement with the results of a study reported previously.[3] In our study, the number of HCC patients classified as advanced cirrhosis was greater than the number with Child-Pugh A. This result is in contrast with the previous study conducted in the Southern region of Turkey.[11] Most of our patients had advanced stage HCC disease and 19% of the patients (n=42) had extrahepatic metastasis.

There is a substantial geographical variation for the etiological causes of HCC throughout the world.[1-5,8-12] Even among Asian countries, the proportion of viral etiology is different, with HCV playing a major role in Japan, whereas the dominant agent is HBV in other Asian countries. HBV is the main etiologic agent of HCC in developing countries, whereas HCV infection predominates in developed countries.[15]

This retrospective study indicates that HBV infection is the leading cause of HCC in our region followed by HDV infection. Forty-five percent of our patients had HBV infection alone, 29% had HDV co-infection, 15% had HCV infection and 10% were idiopathic cases with unknown etiology. In addition to HBV infection, hepatitis delta virus has a substantial role in the development of HCC in our region, which leads to the conclusion that revision of the new regulations are required to pre-

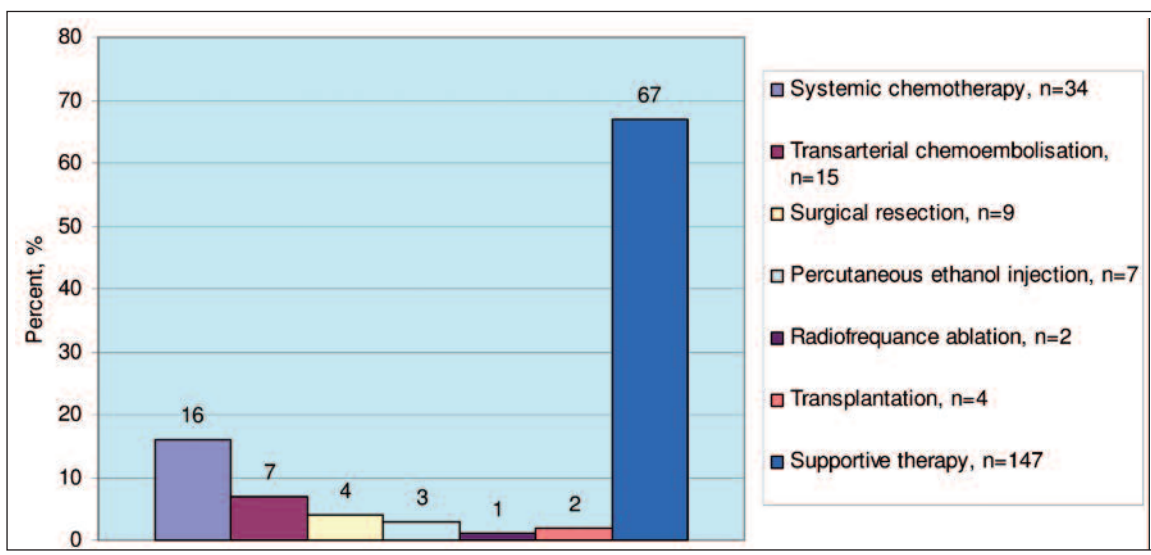

FIGURE 4: The treatment modalities of patients (n=218).
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vent HCC in our country. Moreover, this study suggested that, in contrast to the western societies, alcohol and chronic HCV infection were less important etiological factors.

The majority of HCC patients was negative for HBeAg and had decompansated liver diseases. This finding suggests that advanced liver disease is a well-known risk factor for HCC.[16] Moreover, it is important to monitor all high-risk patients including males, cirrhotics older than 45 years, patients with HBV and HDV infections irrespective of their HBeAg status, and those with advanced cirrhosis.

Early detection of HCC allows the use of potentially curative therapies. USG and AFP screening in patients with cirrhosis have a positive impact on survival.[12,17] In our study, in 64% of patients AFP was higher than 300 ng/ml, in 17% between 10-300 ng/ml, and in 19% lower than 10 ng/ml. These findings were comparable with the results of previous studies[18] and they suggest that HCC cases in our region have relatively higher levels of AFP and more advanced disease. Moreover, low AFP levels in 19% of cases suggest that HCC diagnosis would be missed in this patient group.

The diagnosis was made by liver biopsy in 33% of the patients (n=73) in this study but the role of liver biopsy in hepatocellular carcinoma has become a controversial issue because advances in imaging technology have allowed highly specific identification of these lesions, and in the case of hepatocellular carcinoma, biopsy carries a risk of needle-track seeding.[19]

There are several staging systems to stage HCC patients. The current classifications most commonly used for hepatocellular carcinoma are the Okuda stages, tumor node metastasis (TNM) staging, the Cancer of the Liver Italian Program (CLIP) score, Barcelona Clinic Liver Cancer (BCLC), and Japanese Integrated System (JIS).[20] We used the Okuda system in our study; 11% of the patients had Okuda stage 1, 55% Okuda stage 2, and 34% Okuda stage 3.

The surgical resection is preferred for peripheral and solitary lesions smaller than 5 cm and is tolerated better in Child A cirrhosis, as compared to Child B and C. In patients with Child A cirrhosis, one-year, 2-year and 5-year survival after surgical resection is 55-80%, 42-49%, and 25-39%, respectively.[21] Liver transplantation may be a curable treatment option for HCC. If Milan criteria are followed in the non-resectable patients, 5-year survival after liver transplantation is 70-75 %.[22] The transplantations performed according to the expanding Milan criteria have similar success rates.[23]

In this study, the treatment modalities were noted in only 71 (33%) patients. Thirty-four patients received systemic chemotherapy. Nine underwent surgical resection, and 4 had liver transplantation. The number of patients who underwent TACE, PEI and RF were 15, 7, and 2, respectively. The majority of the patients (n=147) did not have a chance for radical therapies and had supportive therapy only. Only 22 patients had a chance for curative therapy. Curative methods for HCC such as resection and liver transplantation could be used in 5% and 10-15% of cases, respectively in the world literature. This study suggests that, most of the HCC patients do not have a chance for curative therapy. The local and ablative therapies are generally used for palliation, and they result in better outcomes in selected patients.[24-26] Therefore, palliative treatment methods on survival are becoming increasingly important.

Interestingly, there was no decreased level of platelets, as expected to be low in liver cirrhosis. This is partially due to the acute phase reactant feature of platelet, which is common in malignant diseases.

In conclusion, chronic HBV and HDV infections are still the major etiological factors for the development of HCC in our region.[27-29] The etiology of HCC parallels with the prevalence of viral infections in previously conducted studies, which show clearly a high prevalence for HBV[30] and HDV infections[31,32] and low prevalence for HCV infection[33] in our region. Thus, HBsAg carriage continues to be an important risk factor for HCC in Turkey. Although the prevalence of delta virus

infection seems to decrease worldwide, it still has clinical significance in our region.[34] Thus, a national vaccination program and close monitoring and treatment of patients with chronic hepatitis B infection are required to reduce the risk of HCC since sustained reduction of HBV replication lowers the risk of HCC in HBV-related cirrhosis.[4,29] In addition, surveillance strategies of hepatitic and cirrhotic patients for the early diagnosis of HCC is crucial.[35-37]

The majority of the cases had advanced stage disease and extensive involvement in this study. In addition, factors as older age, male sex and advanced liver cirrhosis were important risk factors for HCC. Therefore, especially the cirrhotic patients have to be monitored closely, and the diagnostic methods should be used more effectively. This makes it necessary to develop and use effective diagnostic and treatment methods with efficient screening and monitoring programs in our country.

REFERENCES

1. Stroffolini T. Etiological factor of hepatocellular carcinoma in Italy. Minerva Gastroenterol Dietol 2005;51(1):1-5.
2. Trinchet JC, Alperovitch A, Bedossa P, Degos F, Hainaut P, Beers BV. [Epidemiology, prevention, screening and diagnosis of hepatocellular carcinoma]. Bull Cancer 2009;96(1): 35-43.
3. Sakar B, Ustuner Z, Karagol H, Aksu G, Camlica H, Aykan NF. Prognostic features and survival of inoperable hepatocellular carcinoma in Turkish patients with cirrhosis. Am J Clin Oncol 2004;27(5):489-93.
4. Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127(5 Suppl 1):S35-50.
5. El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 2002;35(5 Suppl 2):S72-8.
6. Llovet JM. Updated treatment approach to hepatocellular carcinoma. J Gastroenterol 2005; 40(3):225-35.
7. Taieb J, Barbare JC, Boussaha T, Cunha AS, Baere Td, Rosmorduc O, et al. [Management of hepatocellular carcinoma. Where are we now? What's next?]. Bull Cancer 2009;96(1): 19-34.
8. Kim SR, Kudo M, Hino O, Han KH, Chung YH, Lee HS; Organizing Committee of Japan-Korea Liver Symposium. Epidemiology of hepatocellular carcinoma in Japan and Korea. A review. Oncology 2008;7 (Suppl 1):13-6.
9. Uzunalimoğlu O, Yurdaydin C, Cetinkaya H, Bozkaya H, Sahin T, Colakoğlu S, et al. Risk factors for hepatocellular carcinoma in Turkey. Dig Dis Sci 2001;46(5):1022-8.
10. Lehman EM, Wilson ML. Epidemiology of hepatitis viruses among hepatocellular carcinoma cases and healthy people in Egypt: a systematic review and meta-analysis. Int J Cancer 2009;124(3):690-7.
11. Ozer B, Serin E, Yilmaz U, Gümürdülü Y, Saygili OB, Kayaselçuk F, et al. Clinicopathologic features and risk factors for hepatocellular carcinoma: results from a single center in southern Turkey. Turk J Gastroenterol 2003;14(2): 85-90.
12. Marrero CR, Marrero JA. Viral hepatitis and hepatocellular carcinoma. Arch Med Res 2007;38(6):612-20.
13. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35(3):421-30.
14. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56(4):918-28.
15. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365(12):1118-27.
16. Umoh NJ, Lesi OA, Mendy M, Bah E, Akano A, Whittle H, et al. Aetiological differences in demographical, clinical and pathological characteristics of hepatocellular carcinoma in The Gambia. Liver Int 2011;31(2):215-21.
17. Daniele B, Bencivenga A, Megna AS, Tinessa V. Alpha-fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology 2004;127(5 Suppl 1): S108-12.
18. Jia HL, Xing XJ, Ye QH, Qin LX. [Application of alpha-fetoprotein in the diagnosis of hepatocellular carcinoma]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2008;30(4):440-3.
19. Rougier P, Mitry E, Barbare JC, Taieb J. Hepatocellular carcinoma (HCC): an update. Semin Oncol 2007;34(2 Suppl 1):S12-20.
20. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003;38(3):207-15.
21. Grazi GL, Cescon M, Ravaioli M, Ercolani G, Gardini A, Del Gaudio M, et al. Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre. Aliment Pharmacol Ther 2003; 17(Suppl 2):119-29.
22. Steinmüller T, Jonas S, Neuhaus P. Review article: liver transplantation for hepatocellular carcinoma. Aliment Pharmacol Ther 2003; 17(Suppl 2):138-44.
23. Freeman RB Jr. Transplantation for hepatocellular carcinoma: The Milan criteria and beyond. Liver Transpl 2006;12(11 Suppl 2): S8-13.
24. Santambrogio R, Podda M, Zuin M, Bertolini E, Bruno S, Cornalba GP, et al. Safety and efficacy of laparoscopic radiofrequency ablation of hepatocellular carcinoma in patients with liver cirrhosis. Surg Endosc 2003;17(11): 1826-32.
25. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362(9399):1907-17.
26. Forner A, Hessheimer AJ, Isabel Real M, Bruix J. Treatment of hepatocellular carcinoma. Crit Rev Oncol Hematol 2006;60(2):89-98.
27. Ozyilkan O, Arslan M, Ozyilkan E. Hepatitis B virus and hepatitis C virus infections in Turkish patients with hepatocellular carcinoma. Am J Gastroenterol 1996;91(7):1479-80.
28. Alacacioglu A, Somali 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):683-8.

29. Yalcin, K, Degertekin H, Bahcecioglu IH, Demir A. Risk factors, clinical and virological characteristics of hepatitis delta virus infection in Turkey. J Hepatol 2003; 38(Suppl 2):183.

30. Mehmet D, Meliksah E, Serif Y, Gunay S, Tuncer O, Zeynep S. Prevalence of hepatitis B infection in the southeastern region of Turkey: comparison of risk factors for HBV infection in rural and urban areas. Jpn J Infect Dis 2005;58(1):15-9.

31. Değertekin H, Yalçin K, Yakut M, Yurdaydin C. Seropositivity for delta hepatitis in patients with chronic hepatitis B and liver cirrhosis in Turkey: a meta-analysis. Liver Int 2008; 28(4):494-8.

32. Bahcecioglu IH, Aygun C, Gozel N, Poyrazoglu OK, Bulut Y, Yalniz M. Prevalence of hepatitis delta virus (HDV) infection in chronic hepatitis B patients in eastern Turkey: still a serious problem to consider. J Viral Hepat 2011;18(7):518-24.

33. Dursun M, Ozekinci T, Ertem M, Saka G, Yilmaz S, Canoruc F, et al. Prevalence of Hepatitis C in adults in the south-eastern region of Anatolia: a community-based study. Hepatol Res 2004;29(2):75-80.

34. Yurdaydin C. Delta hepatitis in Turkey: decreasing but not vanishing and still of concern. Turk J Gastroenterol 2006;17(1):74-5.

35. Yang JD, Kim WR. Surveillance for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2012;10(1): 16-21.

36. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30(1):37-47.

37. Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9(1):64-70.