original article

Clinicopathologic characteristics and outcomes of hepatocellular carcinoma associated with chronic hepatitis B versus hepatitis C infection

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BACKGROUND: Hepatocellular carcinoma (HCC) is a primary liver malignancy and one of the most common cancers worldwide. Few studies in Saudi Arabia have compared the clinicopathologic characteristics of HCC caused by hepatitis B virus (HBV) versus hepatitis C virus (HCV) and their effect on patient survival and prognosis.

OBJECTIVES: Identify differences in clinicopathological characteristics and outcomes of hepatocellular carcinoma (HCC) caused by HBV versus HCV.

DESIGN: A retrospective medical records review.

SETTING: Tertiary medical center in Riyadh.

PATIENTS AND METHODS: We included all new cases of HCC with underlying HBV and HCV infection diagnosed between January 2013 and September 2017 that met inclusion criteria.

MAIN OUTCOME MEASURES: Clinical, biochemical, pathological and radiological characteristics, and survival differences were compared between HCC that developed in HBV- and HCV-infected patients.

SAMPLE SIZE: Of 253 patients evaluated, 172 patients were included in the study.

RESULTS: Of the 172 patients, 110 (64%) had HCV-associated HCC and 62 (36%) had HBV-associated HCC. More patients with HBV infection were males (*P*=.003) and were younger (*P*=.015) than HCV patients. HCV-infected patients who developed HCC had more advanced cirrhosis (*P*=.048). The prevalence of comorbidities and pre-existing cirrhosis was similar in both groups. Seven patients (6.8%) with underlying HCV developed HCC in the absence of cirrhosis. Patients with HBV-associated HCC were less likely to meet Milan criteria at initial diagnosis than those with HCV-associated HCC (33.9% vs. 52.7%, respectively, *P*=.017). HBV-associated HCC occurred at a more advanced Barcelona Clinic Liver Cancer stage. The overall median survival and treatment outcome for each modality was comparable.

CONCLUSIONS: HBV- and HCV-associated HCC have distinct clinical and pathological characteristics, necessitating different screening policies to optimize HCC surveillance and management. However, viral etiology did not affect the treatment outcome and long-term survival.

LIMITATIONS: Conducted in a single-center, retrospective and lacks information about the use of antiviral treatment.

CONFLICT OF INTEREST: None.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide. It is ranked the sixth most common malignancy and the second foremost cause of cancer-related mortality causing approximately 1% of all deaths globally.[1-3] Chronic viral hepatitis B and chronic hepatitis C are among the major risk factors for the development of HCC;[2,3] however, the incidence of HCC varies by geographical region, which has been attributed to the changing distribution and the natural history of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in each region.[4-6] Overall, about 80% to 90% of HCC develops after established liver cirrhosis, irrespective of the cause.[2,5,7] Worldwide, nearly 80% of HCC is associated with HBV and HCV infections.[5,8] HBV as an underlying cause for HCC development is more common in areas where HBV is endemic, like parts of Africa and Asia,[7,9,10] while in the United States, Europe and the Middle East, HCV is the commonest underlying etiology.[11-14] More than half of new cases of HCC in the US are due to HCV. HBV is the major underlying cause for HCC development across the rest of the world and is assumed to be the underlying etiology in nearly 50% of all HCC cases.[15] Most HBV-related HCC develops following liver cirrhosis, but some HCC cases may develop without the presence of cirrhosis.[5,16] HBV patients with cirrhosis have a higher annual incidence of HCC development, as high as 3.16/100 person-years compared to 0.1/100 person-years in those without cirrhosis.[17] An estimated 257 million people are affected by HBV. About 887 000 reported deaths in 2015 were due to HBV and its complications including HCC.[18] HBV infection constitutes only 5% of new HCC cases in the US.[13] The majority of HCC cases develop in patients with HCV infection with preexisting cirrhosis or less commonly in patients who have a significant degree of fibrosis.[19] Globally, about 71 million people are estimated to have chronic hepatitis C and a significant number of those will eventually develop cirrhosis, liver failure or HCC.[20,21] HCV has raised significant concerns internationally for its overwhelming influence on morbidity and mortality.[21-23] Recently, the Global Health Sector Strategy on Viral Hepatitis was adopted by the World Health Assembly to eradicate viral hepatitis and implement global targets to reduce new infections and related deaths by 90% and 65%, respectively by the year 2030.[24,25] In Saudi Arabia, HCC is rated sixth in Saudi males and ninth in Saudi females among cancers of all causes, with an age-standardized incidence rate of 4.8/100 000 for males and 2.4/100 000 for females.[26] The reported median age at diagnosis in males is 68 years (ranged between <1 and 102 years) and in females is 64 years (ranged between 0 and 100 years). As reported globally, more than 75% of HCC cases in Saudi Arabia are attributed to viral hepatitis (hepatitis B and C) with a more recent predominance of HCV over HBV compared to previous reports.[14,27] Existing reports on the effect of HBV and HCV on the overall outcome of HCC are inconsistent. Additionally, few studies have compared the clinicopathologic characteristics of HCC in patients with chronic viral hepatitis and their influence on patient survival and prognosis.[28,29] However, regional and local studies that have addressed the differences between HBV and HCV on HCC outcome are scarce. In this study, we aimed to evaluate the significant clinical characteristics and to assess differences in outcomes in patients chronic liver disease caused by HBV and HCV that developed HCC.

PATIENTS AND METHODS

This study included all cases with a diagnosis of HCC who presented at our center between January 2013 and September 2017. Based on available local and international guidelines, the diagnosis was based on: (1) liver tumor biopsy and (2) cirrhotic liver, with lesions of more than 1 centimeter in diameter, and at least one medical image (dynamic CT-scan or MRI) showing definite early arterial enhancement and venous washout of the lesion. All patients with either HBV or HCV as the underlying etiological risk were included in the analysis. Patients with other non-viral hepatitis etiological risk factors, those with HBV and HCV co-infection, a liver neoplasm (benign or malignant) and non-HCC were excluded. The study was approved by the research center at our institution.

Data collected included demographics, associated comorbid illnesses, hematological and biochemical blood parameters, the causes of the chronic liver disease and documentation of liver cirrhosis. Liver cirrhosis was substantiated by liver biopsy findings, by radiological characteristics, by laboratory tests indicative of severe synthetic hepatic dysfunction and physical and clinical examination suggestive of chronic liver disease. We searched also for associated portal hypertension changes. We used the Model for End-stage Liver Disease (MELD) score and the Child-Turcotte Pugh (CTP) classifications to assess the severity of cirrhosis. We recorded the HCC characteristics: tumor number (HCCs were classified into solitary lesions, two lesions and multiple tumors) and the tumor size (according to the highest dimension of the tumor and in cases of multiple tumors, the largest one was selected for measurement). The following data were also obtained: the date of HCC diagnosis, clinical presentation of HCC, the presence of vascular invasion, portal vein tumor

thrombosis (PVTT), extrahepatic spread, modality of first intervention; the death date, the last date of follow-up and patient survival in years. For better evaluation of the original modes of treatment, treatment strategies were classified into: 1) surgical resection, 2) local ablation; radiofrequency ablation and percutaneous ethanol injection, 3) chemoembolization; trans-arterial chemoembolization and transarterial radioembolization, 4) systemic chemotherapy or 5) palliative therapy. If the patient received no treatment, the original treatment method was considered palliative. We applied the Barcelona Clinic Liver Cancer (BCLC) staging classification to estimate the best potential treatment strategy for HCC patients.[30] Survival, mortality and the cause of death were obtained from the latest notes in the patient chart. A survival census was made on 12 September 2017. We defined the survival as the time between the first date of HCC diagnosis and either the date of death that was related to the HCC or the last clinic follow-up visit on or before 12 September 2017.

Data management and statistical analyses were performed with IBM SPSS version 21.0. Baseline descriptive data were reported as mean and standard deviation (SD) for continuous variables or as frequencies and percentages for categorical variables. Categorical variables were compared between the two groups using the chi-square test. The independent *t* test was used to compare continuous variables. The Mann-Whitney U test was used for comparison of non-parametric data as appropriate. We used uni- and multivariate analyses to describe prognostic indicators for survival. The Kaplan–Meier method was used to produce survival curves and the log-rank test to compare the differences in the survival rates between the groups. Multivariate Cox regression was used to assess prognostic factors for survival. Statistical significance was defined by a *P* value <.05.

RESULTS

Of 253 records, 172 patients met the inclusion criteria. There were 110 patients (64%) with HCV-associated HCCs and 62 patients (36%) with HBV-associated HCCs (**Table 1**). The mean age upon initial diagnosis of patients in the HBV group was younger than that of patients in the HCV group (*P*=.015). There was a statistically significant difference in gender ratio (*P*=.003). HCC developed predominantly among males in both groups, but was more predominant in the HBV group. Although HCC in both groups tended to occur in overweight patients as manifested by high mean of body mass index (BMI), there was no statistically significant difference between the two groups (*P*=.951). There was also no statistically significant difference between the two groups in the presence of ascites, jaundice or symptoms (**Table 1**). For evaluation of the severity of cirrhosis by the CTP score, about half of the cases were class B and C patients in HCV-related HCCs (40.9% and 8.2% respectively), while only about 35% of HBV-related HCCs were of class B and C (22.6% and 12.9% respectively). There was a statistically significant difference among the different CTP classes between both groups (*P*=.05). The mean MELD score was similar in both groups (*P*=.72). Comorbidities were similar between groups although the HCV group tended to have more comorbid conditions, this did not reach statistical significance. At the time of diagnosis, most HCV-related HCCs were asymptomatic (53.6%) compared with HBV-related HCCs (46.8%) (*P*=.39). The symptomatic cases frequently presented with abdominal pain (35.5% in HBV and 23.6% in HCV), abdominal distension (14.5% in both groups) and anorexia (11.3% in HBV and in 13.6% HCV). The presence of liver cirrhosis was similar in both groups. The rate of the non-cirrhotic liver in the HBV group was double that in HCV group (13.80% vs. 6.80%), but the difference was not significant (*P*=.14). However, we found 7 cases (6.8%) of patients with HCV that developed HCC without underlying cirrhosis. In patients with HCV-associated HCC we found significantly lower serum albumin levels compared with HBV patients (*P*=.003). Further, in HCV patients, the mean ALT, AST and platelets levels were lower than those with HBV infection, but this did not reach statistical significance difference. The mean bilirubin levels, prothrombin time and INR were similar in both groups. The mean serum alpha-fetoprotein (AFP) level was high in both groups, but there was no significant difference noticed in HBV-related HCC compared with HCV-related HCC (*P*=.724).

At the time of diagnosis, we found similar tumor numbers in both groups (**Table 2**). Most HCCs were solitary regardless of the underlying etiology of cirrhosis (HBV 43.5% compared to 50.9% in HCV). However, HCV-related HCCs tended to present as solitary nodules of 3 centimeters or less (62.5%), while HBV-related HCCs usually presented as solitary nodules of more than 3 centimeters (66.6%). Tumors of 5 centimeters or more (5 centimeters in greatest cross-sectional diameter) were found in 44.4% of HBV cases but only in 21.4% of HCV patients. HBV patients tended to have larger tumors compared to the HCV patients (*P*=.009). In comparison with HCV-related HCCs, HBV-related HCCs usually present with more locally advanced disease including PVTT and macro-vascular invasion. However, this difference was not statistically significant (*P*=.28 and *P*=.07, respectively). The incidence of distant metastases was more frequent in HBV patients than in HCV patients,

Table 1. Baseline demographic, clinical and biochemical characteristics of hepatocellular carcinoma in patients infected with HBV and HCV (n=172).

		HBV infection		HCV infection		*P* value
		Number	Percent	Number	Percent	
		62	36.0	110	64.0	
Age (years) (mean, SD		61.0 (10)		65.0 (9)		
Gender	Female	11	17.7	44	40.0	**.015**
	Male	51	82.3	66	60.0	**.003**
BMI (mean, SD)		27.63 (7.09)		27.69 (5.53)		.951
CTP score	A	40	64.5	56	50.9	**.048**
	B	14	22.6	45	40.9	
	C	8	12.9	9	8.2	
MELD score (mean, SD)		11.6 (5.29)		11.31 (5.29)		.728
Asymptomatic		29	46.8	59	53.6	.387
Abdominal pain		22	35.5	26	23.6	.960
Abdominal distention		9	14.5	16	14.5	.996
Jaundice		4	6.50	10	9.10	.543
Non-cirrhosis		8	13.80	7	6.80	.143
Diabetes mellitus		30	48.4	69	62.7	.068
Hypertension		26	41.9	63	57.3	.053
Dyslipidemia		7	11.3	12	10.9	.939
Chronic kidney disease		1	1.6	10	9.1	.054
Bilirubin (mmol/L) (mean, SD)		44.5 (59.0)		45.2 (155.5)		.973
Albumin (g/L) (mean, SD)		35.0 (7)		32.0 (6)		**.003**
AST (U/L) (mean, SD)		123.0 (155)		64.0 (64)		.10
ALT (U/L) (mean, SD)		83.0 (94)		60.0 (37)		.078
INR (mean, SD)		1.3 (0.3)		1.3 (0.6)		.883
AFP (ng/mL) (mean, SD)		8099.2 (25)		11004.2 (61)		.724

HBV: hepatitis B virus; HCV: hepatitis C virus; SD: standard deviation; BMI: body mass index; CTP: Child-Turcotte-Pugh score; MELD: model for end-stage liver disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; AFP: alpha-fetoprotein.

Table 2. Radiological and clinical characteristics of hepatocellular carcinoma in patients with HBV and HCV infection.

		HBV		HCV		*P* value
		Number	Percent	Number	Percent	
Number of tumor	Single	27	43.5	56	50.9	.635
	Two lesions	9	14.5	15	13.6	
	Multiple (≥ 3)	26	41.9	39	35.5	
Tumor size (mean, sd)		6.99 (6.36)		4.62 (3.98)		**.009**
Within Milan criteria		21	33.9	58	52.7	**.017**
PVTT		11	17.7	13	11.8	.282
Vascular invasion		10	16.1	8	7.3	.068
Metastasis		10	16.1	12	10.9	.325
BCLC stage	0	2	3.20	4	3.60	.106
	A	17	27.40	51	46.40	
	B	21	33.90	33	30.00	
	C	14	22.60	13	11.80	
	D	8	12.90	9	8.20	

HBV: hepatitis B virus; HCV: hepatitis C virus; SD: standard deviation; PVTT: portal vein tumor thrombosis; BCLC: Barcelona Clinic Liver Cancer. Staging classification, comprises four stages: Stage 0 (very early stage), Stage A (early stage), Stage B (intermediate stage), Stage C (advanced stage) and Stage D (end-stage terminal disease).

but not statistically different (*P*=.325). A larger number of patients with HCV-associated HCC met Milan criteria at initial diagnosis than those with HBV-associated HCC (*P*=.01). As per the BCLC staging classification, HBV-associated HCCs were more advanced than HCV-associated HCCs, but there were no statistically significant differences between different stages in both the groups (*P*=.106). There were 5 patients (8.1%) with HBV-related HCC compared to 11 (10.0%) with HCV-related HCC received liver transplant (*P*=.675).

In the Cox regression, several factors were associated with a negative impact on survival: advanced age, ascites, development of metastasis, vascular invasion, portal vein thrombosis, high AFP of more than 400 ng/mL, multifocal tumor (3 or more), high CTP and MELD scores, non-transplant candidacy (not within Milan criteria) and having undergone chemo-palliative intervention. The presence of underlying chronic hepatitis B, the development of metastasis, high AFP more than 400 ng/mL, non-transplant intervention, mainly chemoembolization and chemopalliative therapy, were significantly poor prognostic factors. The overall median survival from time of diagnosis was 2.3 years. Moreover, the difference in median survival between HBV- and HCV-related HCC was only marginal and not statistically significant (*P*=.63) (**Figure 1**). Survival analysis of the intervention modality showed no significant difference by underlying hepatitis virus (after surgical intervention; *P*=.54, ablation; *P*=.69, chemoembolization; *P*=.97, chemopalliative; *P*=.29). The 1-, 3- and 5-year cumulative survival rates in HBV were 64.5%, 54.8% and 48.4%, respectively, while the 1-, 3- and 5-year cumulative survival rates in HCV were 65.5%, 51.8% and 49.1%, respectively. The overall survival difference between HBV and HCV patients was not affected by the BCLC stages (*P*=.27). However, the survival rate was better for HBV patients than HCV patients in those in stage D (*P*=.038).

DISCUSSION

We observed that although HBV- and HCV-associated HCC have common features, they tend to exhibit distinguishable features in clinical characteristics and presentation. When first diagnosed, most of the patients had good synthetic function. However, more patients with HCV-related HCC had advanced liver disease and had significantly lower serum albumin than HBV-infected patients. Lower serum albumin has recently emerged as

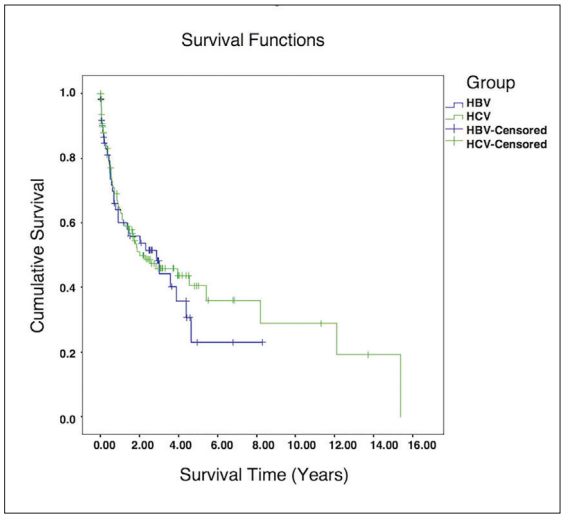

Figure 1. Survival for HBV- and HCV-related HCC patients (*P*=.63).

a significant prognostic HCC indicator as it was found to be linked to the inhibition of HCC progression.[31] In contrast, AFP production does not appear to be associated with a specific viral etiology.

Notably, in our study about half of the patients were diagnosed with HCC as a solitary lesion. Tumors the size of 3 centimeters or less were more frequently seen with HCV-infected individuals (62.5%) than HBV-infected (33.3%). In our study, HBV-related HCC usually presents as a solitary nodule more than 3 centimeters in about two-thirds of patients. We found that HCV-related HCC patients were more likely to be within Milan criteria at the time of diagnosis than those with HBV-associated HCC. This probably explains the numerically higher, but statistically insignificant, number of liver transplantations in this subgroup as compared to HBV. On the other hand, more patients with HBV-associated HCC had a tumor size of >5 centimeters (44%) than those with HCV-associated HCC. In Barazani et al, 56% of HBV patients as compared to 18% of HCV patients had tumors larger than 5 centimeters and were beyond the Milan criteria when considered for liver transplant (*P*=.028), which is in keeping with our results.[32] Macrovascular invasion and metastases developed more frequently in HCC patients associated with HBV; nonetheless, this finding did not attain a statistical significance. In the current study, we found generally poor overall survival with no significant differences in survival in relation to the viral etiology. In adjusted analyses, factors associated with overall poorer survival included advanced liver disease, chronic kidney disease and lack of HCC curative procedures. On further stratification with viral status, the presence of metastasis, high AFP>400 and non-transplant intervention was associated with poor outcome in the HBV group. Given the high HCC-related mortality, with only 35% of patients being a candidate for potentially curative treatment, the overall poor survival remains significant in our cohort. Consistent with our findings, Kitisin et al in a large series of HCC patients, reported that only 29.5% of patients were deemed candidates for curative therapies.[33]

HCV infection was the the dominant risk factor for HCC in in our study, being nearly twice (1.8:1) as common as HBV infection, which is consistent with previously published studies from Saudi Arabia.[14,27] On the contrary, in Eastern Asia and Sub-Saharan Africa, the major cause of HCC remains chronic hepatitis B infection.[34] HBV has been previously considered endemic in Saudi Arabia, but after the mass immunization program commenced in 1989, a significant decline occurred in the disease burden in this population, which may explain the lower prevalence of HBV-related HCC seen in this study.[35] Both viral infections are usually acquired by horizontal transmission in Saudi Arabia. In contrast to HBV, HCV exposure occurs primarily due to exposure to infected body fluids in high-risk populations later in life.[36] This finding potentially highlights the distinct age difference at which the diagnosis of HCC was initially established in our cohort, demonstrating that HBV patients were diagnosed at a younger age in comparison to patients with HCV, which is quite similar to observations in Japanese studies.[37] Patients with HBV infection can develop HCC even without cirrhosis, particularly younger patients with fairly preserved hepatic reserves. This may result in a late diagnosis that would eventually affect the prognosis, as the tumor would be more advanced and the patient more unsuited to liver transplantation. Several studies have shown that patients who develop HCC at a younger age were probably missed in a surveillance program for HCC and were seen at an advanced cancer stage.[38,39] Inconsistent HCC surveillance practiced in Saudi Arabia for HBV- and HCV- infected individuals could also be responsible for this observation. Other differentiating characteristics of HCC progression between HBV and HCV patients include the association between diabetes and alpha-fetoprotein production. Patients infected with HCV infection have a higher risk of diabetes than those infected with HBV, with some reports showing that diabetes and HCV jointly aggravate the risk of HCC.[40,41] We observed more patients in the HCV group with metabolic syndrome, but it failed to reach statistical significance, probably due to the high prevalence of diabetes and obesity in Saudi Arabia.[42] In our study, the rate of diabetes and the mean serum AFP level were high in both groups, however, there was no

significant difference between HBV- and HCV-related HCC. Interestingly, we observed 7 patients in the HCV group who developed HCC in a non-cirrhotic liver. HCC occurrence in the absence of cirrhosis is an established feature of chronic hepatitis B.[16,17] We found that a similar number of HCV patients developed HCC compared to HBV patients in the absence of cirrhosis, but the percentage of HBV infected was twice that of the HCV infected cases. The risk of HCC in HCV-infected individuals without cirrhosis has a prevalence of 16% to 30%.[43,44] The likelihood of HCC development in patients without advanced fibrosis may suggest the presence of other components in the pathological process of HCV that are not yet understood.[44] Several studies have documented a significant risk reduction for HCC when patients achieved sustained viral clearance with interferon treatment.[45-47] However, the natural course of HCC in patients with cirrhosis was not altered by the recent introduction of direct-acting antivirals and initial studies have proposed a possible increase in developing a de novo or recurrence of previously treated HCC.[48,49] This raises the crucial question of the need to perform follow-up of these patients, even after cure. The burden of HCC continues to increase globally, driven by the HBV- and HCV-infected population. However, the introduction of new and highly effective antiviral treatments for HCV and implementation of the HBV vaccine should slow the advancement of chronic hepatitis due to HBV and HCV into cirrhosis with the consequent development of HCC. On the other hand, obesity, non-alcoholic fatty liver disease and resulting nonalcoholic steatohepatitis are increasing the risk of HCC in the Western world.[50,51]

The conclusions of our study are limited because it is retrospective, lacks information about the use of antiviral treatment, and was from a single center. In conclusion, HBV- and HCV-associated HCC have distinct clinical and pathological characteristics. These differences necessitate different screening and treatment policies to optimize HCC surveillance and management and controlling risk factors like obesity and insulin resistance. Identification of high-risk groups for surveillance, early detection, and treatment of HCC is also important.

REFERENCES

1. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015; 19: 223-238.
2. Balogh J, Victor D 3rd, Asham EH, Burroughs SG, Boktour M, Saharia A, et al. Hepatocellular carcinoma: a review. J Hepatocell Carcinoma. 2016; 3:41-53.
3. Zhu RX, SetoWK, Lai CL, Yuen MF. Epidemiology of Hepatocellular Carcinoma in the Asia-Pacific Region. Gut Liver. 2016; 10:332-9.
4. Liu CJ, Kao JH. Hepatitis B virus-related hepatocellular carcinoma: epidemiology and pathogenic role of viral factors. J Chin Med Assoc. 2007; 70: 141-145.
5. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012; 142: 1264–1273.
6. de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology 2015; 62:1190–200.
7. Crissien AM, Frenette C. Current management of hepatocellular carcinoma. Gastroenterol Hepatol (N Y). 2014; 10: 153-161.
8. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006;45(4):529-38.
9. European Association for The Study of The Liver; European Organisation For Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.
10. Hemming AW, Berumen J, Mekeel K. Hepatitis B and Hepatocellular Carcinoma. Clin Liver Dis. 2016; 20: 703-720.
11. Zhang Y, Ren JS, Shi JF, Li N, Wang YT, Qu C, et al. International trends in primary liver cancer incidence from 1973 to 2007. BMC Cancer. 2015; 15: 94.
12. PetrickJL, Braunlin M, Laversanne M, Valery PC, Bray F, McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. Int J Cancer. 2016; 139: 1534-1545.
13. Mittal S, El-Serag HB. Epidemiology of hepatocellular carcinoma: consider the population. J Clin Gastroenterol 2013; 47 Suppl: S2-6.
14. Aljumah AA, Kuriry H, AlZunaitan M, Al Ghobain M, Al Muaikeel M, Al Olayan A, et al. Clinical Presentation, Risk Factors, and Treatment Modalities of Hepatocellular Carcinoma: A Single Tertiary Care Center Experience. Gastroenterol Res Pract. 2016; 2016: 1989045.
15. Parkin, DM. The global health burden of infection-associated cancers in the year 2002. Int J Cancer. 2006; 118: 3030-3044.
16. 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.
17. Thiele, M, Gluud, LL, Fialla, AD, Dahl, EK, Krag, A. Large variations in risk of hepatocellular carcinoma and mortality in treatment naive hepatitis B patients: systematic review with meta-analyses. PLoS One. 2014;9: e107177.
18. World Health Organization [Internet]. Hepatitis B, Fact sheet. (2017). [cited 2018 February 25]. Available from: http://www.who.int/mediacentre/factsheets/fs204/en/.
19. Lok AS, Everhart JE, Wright EC, Di Bisceglie AM, Kim HY, Sterling RK, et al.; HALT-C Trial Group. Maintenance peginterferon therapy and other factors associated with hepatocellular carcinoma in patients with advanced hepatitis C. Gastroenterology. 2011; 140(3):840-9
20. Gane E, Kershenobich D, Seguin-Devaux C, Kristian P, Aho I, Dalgard O, et al. Strategies to manage hepatitis C virus (HCV)infection disease burden- volume 2. J Viral Hepat. 2015;22 Suppl 1:46-73.
21. Chhatwal J, Wang X, Ayer T, Kabiri M, Chung RT, Hur C, et al. Hepatitis C Disease Burden in the United States in the era of oral direct-acting antivirals. Hepatology. 2016;64(5):1442-1450.
22. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016;388(10049):1081-1088.
23. Aljumah AA, Abaalkhail F, Al-Ashgar H, Assiri A, Babatin M, Al Faleh F, et al. Epidemiology, disease burden, and treatment strategies of chronic hepatitis C virus infections in Saudi Arabia in the new treatment paradigm shift. Saudi J Gastroenterol. 2016;22(4):269-81.
24. World Health Organization [Internet]. Draft Global Health Sector Strategies Viral Hepatitis 2016–2021. (2016). [cited 2017 November 16]. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf?ua=1
25. World Health Organization [Internet]. Combating Hepatitis B and C to Reach Elimination by 2030. (2016). [cited 2017 November 16]. Available from: http://www.who.int/hepatitis/publications/hep-elimination-by-2030 brief/en/
26. Saudi Health Council, Saudi Cancer Reg-

istry Cancer Incidence Report, Saudi Arabia [Internet]. (2017). [cited 2017 November 16]. Available from: https://nhic.gov.sa/eServices/Documents/2014.pdf
27. Alswat KA, Sanai FM, Altuwaijri M, Albenmousa A, Almadi M, Al-Hamoudi WK, et al. Clinical characteristics of patients with hepatocellular carcinoma in a middle eastern population. Hepat Mon. 2013;13(5): e7612.
28. Chen CH, Huang GT, Yang PM, Chen PJ, Lai MY, Chen DS, et al. Hepatitis B- and C-related hepatocellular carcinomas yield different clinical features and prognosis. Eur J Cancer. 2006; 42:2524-9.
29. Ng J, Wu J. Hepatitis B- and hepatitis C-related hepatocellular carcinomas in the United States: similarities and differences. Hepat Mon. 2012; 12: e7635.
30. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329-38.
31. Bagirakci E, Sahin E, Erdal E, Guerra V, Carr BI. Role of albumin in growth inhibition in hepatocellular carcinoma. Oncology. 2017; 93:136-142.
32. Barazani Y, Hiatt JR, Tong MJ, Busuttil RW. Chronic viral hepatitis and hepatocellular carcinoma. World J Surg. 2007; 31:1243–8.
33. Kitisin K, Packiam V, Steel J, Humar A, Gamblin TC, Geller DA, et al. Presentation and outcomes of hepatocellular carcinoma patients at a western centre. HPB (Oxford). 2011; 13:712-22.
34. Raza SA, Clifford GM, Franceschi S. Worldwide variation in the relative importance of hepatitis B and hepatitis C viruses in hepatocellular carcinoma: a systematic review. Br J Cancer. 2007; 96:1127–1134.
35. Al-Faleh FZ, Al-Jeffri M, Ramia S, Al-Rashed R, Arif M, Rezeig M, et al. Seroepidemiology of hepatitis B virus infection in Saudi children 8 years after a mass hepatitis B vaccination programme. J Infect. 1999; 38:167-70.
36. Deuffic-Burban S, Abiteboul D, Lot F, Branger M, Bouvet E, Yazdanpanah Y. Costs and cost-effectiveness of different follow-up schedules for detection of occupational hepatitis C virus infection. Gut. 2009; 58:105–110.
37. Tanizaki H, Ryu M, Kinoshita T, Kawano N, Konishi M, Cho A, et al. Comparison of clinical features and survival in patients with hepatitis B and C virus-related hepatocellular carcinoma. Jpn J Clin Oncol. 1997;27(2):67–70.
38. Kim JH, Choi MS, Lee H, Kim DY, Lee JH, Koh KC, et al. Clinical features and prognosis of hepatocellular carcinoma in young patients from a hepatitis B-endemic area. J Gastroenterol Hepatol. 2006; 21:588-94.
39. Wang Q, Luan W, Villanueva GA, Rahbari NN, Yee HT, Manizate F, et al. Clinical prognostic variables in young patients (under 40 years) with hepatitis B virus-associated hepatocellular carcinoma. J Dig Dis. 2012;13(4):214-8.
40. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol. 2006; 4:369– 80.
41. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev. 2012; 28:109-22.
42. De Nicola E, Aburizaiza OS, Siddique A, Khwaja H, Carpenter DO. Obesity and public health in the Kingdom of Saudi Arabia. Rev Environ Health. 2015; 30:191-205.
43. Shim CW, Park JW, Kim SH, Kim JS, Kim BH, Kim SH, et al. Noncirrhotic hepatocellular carcinoma: etiology and occult hepatitis B virus infection in a hepatitis B virus-endemic area. Therap Adv Gastroenterol. 2017;10: 529-536.
44. Yeh MM, Daniel HD-J, Torbenson M. Hepatitis C- Associated Hepatocellular Carcinomas in Non-Cirrhotic Livers. Mod Pathol. 2010; 23:276-283.
45. Nahon P, Bourcier V, Layese R, Audureau E, Cagnot C, Marcellin P, et al. ANRS CO12 CirVir Group. Eradication of Hepatitis C Virus Infection in Patients with Cirrhosis Reduces Risk of Liver and Non-Liver Complications. Gastroenterology. 2017; 152:142-156.e2.
46. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007; 147:677-84.
47. Kobayashi S, Takeda T, Enomoto M, Tamori A, Kawada N, Habu D, et al. Development of hepatocellular carcinoma in patients with chronic hepatitis C who had a sustained virological response to interferon therapy: a multicenter, retrospective cohort study of 1124 patients. Liver Int. 2007; 27:186-91.
48. Reig M, Mariño Z, Perelló C, Iñarrairaegui M, Ribeiro A, Lens S, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016; 65:719-726.
49. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016; 65:727-33.
50. Hashimoto E, Tokushige K. Hepatocellular carcinoma in non-alcoholic steatohepatitis: Growing evidence of an epidemic? Hepatol Res. 2012; 42: 1-14.
51. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. Liver Int. 2017; 37 Suppl 1:81-4.