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ORIGINAL ARTICLE

A study of 3013 cases of hepatocellular carcinoma: Etiology and therapy before and during the current decade

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chronic hepatitis B, epidemiology, hepatocellular carcinoma, non-alcoholic steatohepatitis.

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Abstract

Background and Aim: Hepatocellular carcinoma (HCC) is a significant global problem. With advances in HCC diagnosis and therapy, our hypothesis is that there are significant differences in the clinical characteristics and treatment of HCC over the years.
Methods: Patients with HCC between 1980 and 2018 from three major tertiary hospitals in Singapore were enrolled into a Research Electronic Data Capture database. Clinical characteristics and treatment of HCC were compared between those diagnosed before 2008 (cohort A) and during the current decade (ie from 2008 onwards) (cohort B).
Results: There were 3013 patients. Mean age of HCC diagnosis was significantly older in cohort B (68.6 *vs* 61.2 years, $P < 0.001$). The most common etiology remained as chronic hepatitis B infection but the proportion due to hepatitis B was significantly lower in cohort B (46.6% *vs* 57.2%, $P < 0.0001$). The prevalence of cryptogenic/non-alcoholic steatohepatitis was significantly higher in cohort B than cohort A (27.1% *vs* 18.6%, $P < 0.0001$). More patients received curative therapy in cohort B (43.7% *vs* 27.1%, $P < 0.0001$.
Conclusion: In this largest collection of HCC patients in Singapore, patients are diagnosed with HCC at an older age and cryptogenic/non-alcoholic steatohepatitis is becoming more important as an etiology of HCC in the current decade. More patients also received curative therapy in the current decade.

Introduction

Liver cancer is the third leading cause of cancer death globally, with more than 830 000 deaths in 2020.[1] Hepatocellular carcinoma (HCC) arises as a result of chronic viral hepatitis infection, non-alcoholic steatohepatitis (NASH), excessive alcohol usage, and other causes of chronic liver diseases such as autoimmune hepatitis (AIH) and primary biliary cholangitis (PBC).[2] While viral hepatitis is still the leading cause of cirrhosis and HCC,[3] NASH looks set to overtake viral hepatitis given the global pandemic of growing obesity and sedentary lifestyle.[4,5]

Over the years, there have been advances in the diagnosis and treatment of HCC.[6] The dynamic imaging modalities of computerized tomography (CT) and magnetic resonance imaging (MRI)[7] allow definitive diagnosis of early HCC detected during surveillance with ultrasound,[8] hence improving the chances of curative treatment. The armamentarium of treatment options has also expanded. Besides resection and liver transplantation, locoregional and systemic therapies have also been shown to improve survival.[9] For instance, sorafenib was the only systemic therapy available for advanced HCC in the previous decade but currently there are several agents of different drug classes shown to be efficacious in advanced HCC when used either singly or as a combination therapy.[10] In view of the changing landscape of HCC epidemiology and advances in HCC diagnosis and therapy, we investigated if there are significant differences in the clinical characteristics and therapy of HCC diagnosed before and from 2008 onwards.

Methods

Study population. Patients with HCC from three tertiary hospitals in Singapore (Singapore General Hospital [SGH], Tan Tock Seng Hospital [TTSH], and National University Hospital [NUH]) were prospectively enrolled into a Research Electronic

Data Capture (*REDCap*) database. The cases were accrued from SGH, NUH, and TTSH from 1980, 1999, and 2001, respectively.

This study was approved by the Institutional Review Board (IRB) with a waiver for informed consent as all patients were de-identified.

Data collection. The patient's demographics (gender, age at diagnosis of HCC, and race), etiology of cirrhosis (hepatitis B, hepatitis C, alcohol, cryptogenic/NASH, and other causes such as AIH and PBC), and HCC treatment were recorded into the REDCap database.

The etiology of HCC was hepatitis B virus (HBV) infection if the patient was tested positive for hepatitis B surface antigen. The patient was classified as having HCC related to hepatitis C virus (HCV) infection if antibody serology for hepatitis C (IgG) or HCV RNA was positive. HCC is regarded to be caused by alcohol ingestion when the patient had a daily consumption of more than 60 g of alcohol for at least 10 years in both male and female patients. Patients were considered to have HCC that was of cryptogenic (likely NASH related) etiology when HBV, HCV, alcohol, and other chronic liver diseases (such as AIH and PBC) were excluded.

Treatment modalities for HCC were further divided into curative, palliative, and best supportive care. Curative treatment modalities include surgical resection, percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), and liver transplantation. Palliative modalities include transhepatic arterial chemoembolization (TACE), selective internal radiation (SIRT), sorafenib, or other systemic chemotherapy.

Statistical analysis. The clinical characteristics and treatment modalities of HCC diagnosed before 2008 (Cohort A) were compared with those diagnosed in the current decade from 2008 onwards (Cohort B). Percentages (%) were computed for categorical variables while mean with standard deviation was calculated for continuous variables. Mann–Whitney U test and Chi-square test were performed for continuous and categorical variables, respectively. All statistical analyses were performed using SPSS version 23 (IBM Corp, Armonk, NY, USA). All P values were two-sided and a P value of <0.05 was considered statistically significant.

Results

There were 3017 patients enrolled into REDCap. Four patients were excluded due to incomplete data. In the final count, 3013 patients were included in the study. The overall mean age of HCC diagnosis was 63.8 ± 12.3 years. The mean age at diagnosis of HCC was significantly older in patients in Cohort B compared with Cohort A (68.6 years *vs* 61.2 years, $P < 0.001$). Overall, majority of patients were male (80.5%). Majority was of Chinese ethnicity (84.6%), followed by Malay (7.0%), foreigners (5.6%), and Indian (2.8%). There were significantly more foreigners in Cohort B compared with A (6.7% *vs* 4.3%, $P < 0.007$) (Table 1).

The most common etiology of HCC was chronic hepatitis B (CHB) infection (52.1%), followed by cryptogenic/NASH (22.7%), alcohol (15.4%), chronic HCV infection (9.3%), and other causes (0.5%). Although the most common etiology of HCC was CHB infection in both cohorts, the proportion due to HBV was significantly lower in Cohort B than A (46.6% *vs* 57.2%, $P < 0.0001$). Conversely, the prevalence of cryptogenic/NASH is higher in Cohort B than Cohort A (27.1% *vs* 18.6%, $P < 0.0001$) (Table 2).

Overall, about equal number of patients received either curative therapy or best supportive care (35.7% and 35.4% respectively) (Table 3). Significantly more patients received curative therapy in Cohort B compared with Cohort A (43.7% *vs* 27.1%, $P < 0.0001$) and significantly fewer patients received best supportive care in Cohort B than A (26.8% *vs* 44.7%, $P < 0.0001$) (Table 3). Resection (24.1%) and RFA (10.9%) were

Table 1 Patient characteristics

	Overall	Before 2008 (Cohort A)	From 2008 (Cohort B)	*P* value
Number of patients	3013	1334	1679	
Age at diagnosis (years) mean ± SD	63.8 ± 12.3	61.2 ± 12.6	68.6 ± 11.2	<0.001
Male (%)	2425 (80.5)	1086 (81.4)	1339 (79.7)	0.267
Chinese (%)	2549 (84.6)	1164 (87.3)	1385 (82.5)	1.000
Malay (%)	211 (7.0)	84 (6.3)	127 (7.6)	0.196
Indian (%)	83 (2.8)	28 (2.1)	55 (3.3)	0.057
Foreigners (%)	170 (5.6)	58 (4.3)	112 (6.7)	0.007

Table 2 Etiology of hepatocellular carcinoma

Etiology	Overall	Before 2008 (Cohort A)	From 2008 (Cohort B)	*P* value
Chronic hepatitis B (%)	1280 (52.1)	727 (57.2)	553 (46.6)	<0.0001
Chronic hepatitis C (%)	228 (9.3)	104 (8.2)	124 (10.5)	0.060
Alcohol (%)	379 (15.4)	200 (15.7)	179 (15.1)	0.696
Cryptogenic/non-alcoholic steatohepatitis (%)	557 (22.7)	236 (18.6)	321 (27.1)	<0.0001
Others[†] (%)	13 (0.5)	4 (0.3)	9 (0.8)	0.167

[†]Others include autoimmune hepatitis and primary biliary cholangitis.

Table 3 Overall treatment modalities of hepatocellular carcinoma

Treatment	Overall	Before 2008 (Cohort A)	From 2008 (Cohort B)	*P* value
Curative (%)	787 (35.7)	288 (27.1)	499 (43.7)	<0.0001
Palliative (%)	636 (28.9)	299 (28.2)	337 (29.5)	0.510
Best supportive care (%)	780 (35.4)	474 (44.7)	306 (26.8)	<0.0001

Table 4 Breakdown of treatment modalities of hepatocellular carcinoma

Treatment modality	Number of patients (%)	Remarks
Resection	531 (24.1)	787 (35.7%) underwent curative treatment
Liver transplant	5 (0.2)	
RFA	241 (10.9)	
PEIT	10 (0.5)	
TACE	429 (19.5)	636 (28.9%) underwent palliative treatment
SIRT	35 (1.6)	
Systemic therapy	172 (7.8)	
Best supportive care	780 (35.4)	—

PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transhepatic arterial chemoembolization.

the two most common curative therapies followed distantly by PEIT (0.5%) and liver transplantation (0.2%) (Table 4). There were 636 (28.9%) patients who received palliative therapy. The most common palliative therapy by far was TACE (19.5%), followed by systemic therapy (7.8%) and SIRT (1.6%) (Table 4). The rest of the patients received best supportive care ($n = 780$, 35.4%).

Discussion

This is the largest single collection of HCC reported in Singapore and is also the first study to describe the local treatment landscape. There were significant features in the epidemiology of HCC over the decades, in particular in etiology and therapy. Other significant findings were that the mean age at the time of diagnosis of HCC had increased and a significantly lower proportion was due to CHB infection compared with cryptogenic/NASH even though CHB infection remained the most common etiology. Another significant finding was that more patients received curative therapy in the current decade. One possible explanation for the increase in age at the time of HCC diagnosis is that the availability of hepatitis B antiviral therapies since mid-1990s has delayed the age of development of HCC in HBV patients.[11,12] Unfortunately, we did not collect any HBV treatment data in the database to be able to substantiate this postulation.

There is a higher proportion of male patients with HCC as compared with women, in keeping with all other HCC epidemiological studies.[3,13] This is likely due to the influence of androgens on the development of HCC.[14,15] In addition, men also have higher risk-taking behaviors such as usage of intravenous drugs (which result in a higher exposure to hepatitis C) and alcohol intake.[16] There are also more foreigners diagnosed with HCC in Cohort B as compared with Cohort A, and this is likely due to the growth of Singapore as a regional medical hub.

A large proportion of patients with cryptogenic liver cirrhosis are now recognized to have burn-out NASH cirrhosis.[16,17] Bearing this in mind, we presume that it is reasonable to regard cryptogenic cirrhosis as the surrogate of NASH cirrhosis, and we found that cryptogenic/NASH cirrhosis is increasing in prevalence as an etiology of HCC in our population. This can be explained by the improved socioeconomic status of our population and ensuing increase in prevalence of diabetes and obesity. This trend is also in keeping with that observed in other populations globally.[18] HCC has also been shown to develop in patients with NASH in the absence of cirrhosis.[19] Hence, more effort needs to be put into the study of the NASH such as pharmacological therapies to retard the progress of NASH with resulting HCC.

Our study also showed that the proportion of patients who received curative therapy is significantly higher in Cohort B compared with Cohort A. This is likely the result of earlier diagnosis of HCC from regular surveillance for HCC as our previous study showed that patients with HCC who were diagnosed from 2003 onwards had better Barcelona Clinic Liver Cancer stages,[20] hence more patients were able to undergo curative treatment.

The strength of this study is that it is the largest single study of HCC patients in Singapore. The study population spanned over nearly four decades from all three tertiary hospitals in Singapore. Hence, it is an accurate representation of the epidemiology of HCC in the country. This is also the only study to date that describes the treatment landscape of HCC in Singapore.

The limitations of this study include the lack of data on metabolic syndrome as the latter is a strong indicator for NASH as an etiological entity because the database was started before the appreciation of NASH as an etiology of HCC. Another limitation of this study is that alcohol history was self-reported. To overcome possible underreporting, we adopted a higher threshold of alcohol consumption of more than 60 g/day for more than 10 years before attributing the cirrhosis to alcohol use. The patients enrolled from one of the three hospitals were largely from the surgical department and may potentially bias toward patients amenable to surgical resection.

In conclusion, this is the largest single collection of HCC in Singapore reported to date and it shows CHB infection as the predominant risk factor for HCC throughout the decades. Our previous study has shown that the rate of HCC development in our HBV patients is similar to that reported in other Asian countries.[21] Nevertheless, there is already an increasing importance of NASH/cryptogenic cirrhosis and undoubtedly its prevalence will grow in the near future. Patients were increasingly amenable to curative therapy. However, there still remain a substantial number of patients without any active treatment option, and this is a

strong impetus for a more robust HCC surveillance program in our at-risk population to enable diagnosis of HCC at an earlier treatable stage. Likewise, there should also be more vigilance in identifying and managing patients at risk for NASH.

References

1 Sung H, Ferlay J, Siegel RL *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**: 209–49.

2 Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat. Rev. Gastroenterol. Hepatol.* 2019; **16**: 589–604.

3 Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. *Gastroenterology*. 2019; **156**: 477–91 e1.

4 Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat. Rev. Gastroenterol. Hepatol.* 2021; **18**: 223–38.

5 Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. *Nat. Rev. Gastroenterol. Hepatol.* 2019; **16**: 411–28.

6 Chou R, Cuevas C, Fu R *et al*. Imaging techniques for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Ann. Intern. Med.* 2015; **162**: 697–711.

7 Ronot M, Purcell Y, Vilgrain V. Hepatocellular carcinoma: current imaging modalities for diagnosis and prognosis. *Dig. Dis. Sci.* 2019; **64**: 934–50.

8 Lertpipopmetha K, Tubtawee T, Piratvisuth T, Chamroonkul N. Comparison between computer tomography and magnetic resonance imaging in the diagnosis of small hepatocellular carcinoma. *Asian Pac. J. Cancer Prev.* 2016; **17**: 4805–11.

9 Couri T, Pillai A. Goals and targets for personalized therapy for HCC. *Hepatol Int.* 2019; **13**: 125–37.

10 Kudo M. Recent advances in systemic therapy for hepatocellular carcinoma in an aging society: 2020 update. *Liver Cancer.* 2020; **9**: 640–62.

11 Hosaka T, Suzuki F, Kobayashi M *et al*. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013; **58**: 98–107.

12 Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. *Lancet*. 2018; **392**: 2313–24.

13 Kim HS, El-Serag HB. The Epidemiology of Hepatocellular Carcinoma in the USA. *Curr. Gastroenterol. Rep.* 2019; **21**: 17.

14 El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007; **132**: 2557–76.

15 Omata M, Cheng AL, Kokudo N *et al*. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol. Int.* 2017; **11**: 317–70.

16 Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*. 2004; **127**(5 Suppl 1): S35–50.

17 Margini C, Dufour JF. The story of HCC in NAFLD: from epidemiology, across pathogenesis, to prevention and treatment. *Liver Int.* 2016; **36**: 317–24.

18 Younossi ZM, Marchesini G, Pinto-Cortez H, Petta S. Epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: implications for liver transplantation. *Transplantation*. 2019; **103**: 22–7.

19 Stine JG, Wentworth BJ, Zimmet A *et al*. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment. Pharmacol. Ther.* 2018; **48**: 696–703.

20 Goh GB, Li JW, Chang PE, Chow KY, Tan CK. Deciphering the epidemiology of hepatocellular carcinoma through the passage of time: A study of 1,401 patients across 3 decades. *Hepatol. Commun.* 2017; **1**: 564–71.

21 Poh Z, Goh BB, Chang PE, Tan CK. Rates of cirrhosis and hepatocellular carcinoma in chronic hepatitis B and the role of surveillance: a 10-year follow-up of 673 patients. *Eur. J. Gastroenterol. Hepatol.* 2015; **27**: 638–43.