ORIGINAl ARTICLE

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

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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 [NUHI]) were prospectively enrolled into a Research Electronic Data Capture database.
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 1).

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...
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 genetic/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

## 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.
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.

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