Deciphering the Epidemiology of Hepatocellular Carcinoma Through the Passage of Time: A Study of 1,401 Patients Across 3 Decades

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Hepatocellular carcinoma (HCC) is one of the most common and lethal cancers globally. With advances in therapy for chronic viral hepatitis, changing social circumstances, and increasing practice of HCC surveillance, the epidemiology of HCC is expected to change over time. We explored the temporal trends in HCC in Singapore, a multiethnic Asian country, over the last 3 decades. Patients with HCC were prospectively enrolled and stratified into two cohorts (C1, 1988-2002; C2, 2003-2016). Patient and tumor characteristics, management, and survival were compared between the two cohorts, and a survival census was performed on October 31, 2015. There were 1,401 patients, and the mean age at diagnosis of HCC for C1 and C2 was 60.1 and 63.5 years, respectively. Male patient preponderance decreased significantly, with the male to female ratio falling from 5.2:1 to 3.9:1 between C1 and C2. Hepatitis B, although still the predominant risk factor for HCC, showed a significant decline from C1 to C2 (76.5% to 68.2%), while the nonviral etiology increased significantly over the same period (14.4% versus 25.0%, respectively). Significantly more patients in C2 than C1 were diagnosed through surveillance (39.2% versus 11.3%, respectively) and had better physical performance (Eastern Cooperative Oncology Group 0, 62.1% versus 20.4%, respectively). While Child-Pugh status was comparable, significantly more patients in C2 than C1 had early stage disease (Barcelona Clinic Liver Cancer 0-A, 39.5% versus 7.4%, respectively), which translated into significantly higher median survival (18.6 months versus 3.8 months, respectively). *Conclusion*: Over the past 3 decades, hepatitis B-related HCC has been decreasing while HCC due to nonviral etiology has been increasing significantly. Surveillance to diagnose early stage HCC is important in improving the outcome of HCC. (*Hepatology Communications* 2017;1:564–571)

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. In 2012, HCC had an estimated global incidence of 782,000 cases, representing the fifth most common cancer in male individuals and ninth most common cancer in female individuals.[1] More importantly, HCC is a lethal cancer as it is the second leading cause of cancer deaths globally and accounted for 746,000 deaths worldwide in 2012.[1]

While HCC has traditionally been recognized to have distinct geographic heterogeneity, the global pattern of HCC has undergone substantial changes over the last few decades.[2-4] Increasing incidence of HCC has been observed in regions with traditionally low

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CHB, chronic hepatitis B; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; Ig, immunoglobulin; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RFA, radio frequency ablation.

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prevalence of HCC, such as North America and Europe, while the converse has been reported in high-prevalence regions, such as China.[2,5-7] Nevertheless, the incidence rates in high-prevalence regions remain much higher than those seen in the low-prevalence regions. Changing patient characteristics, including exposure to changing HCC risk factors, dictate the temporal trends in epidemiology of HCC. Equally, improved understanding and advances in management of liver disease, cirrhosis, and HCC have had a positive impact on the outcome of HCC.[8]

Exploration of the epidemiological trends in HCC within Singapore provides a unique vantage point to scrutinize various factors at work. First, Singapore lies within Asia, which is home to 75% of all HCC cases worldwide.[2] Second, the impact of chronic hepatitis B (CHB) as a cause for HCC has been declining due to the implementation of successful nationwide hepatitis B vaccination programs and use of antiviral therapies, as can be reflected in Singapore. Nationwide hepatitis B screening/vaccination programs have been implemented in Singapore since 1987, resulting in a declining hepatitis B seroprevalence.[9] Third, with rapid development, urbanization, and changing lifestyles in Singapore, an increasing prevalence of obesity, diabetes mellitus, hypertension, and dyslipidemia has been reported.[10] As these metabolic risk factors are commonly associated with nonalcoholic fatty liver disease (NAFLD), the prevalence of NAFLD would also be expected to be on the upsurge.[11]

In view of the temporal change in risk factors, we hypothesize that the decline of CHB as a risk factor for HCC may be offset by the emergence of NAFLD as a rising cause of HCC in Singapore. Indeed, in one of the Singaporean community-based cross-sectional studies, 40% of subjects were observed to have NAFLD.[12] The aim of this study is to explore the temporal trends in HCC characteristics and epidemiology that have occurred over the last 3 decades. Appreciation of the epidemiological trends will permit clinicians to anticipate and adapt accordingly in terms of public health perspectives, resource allocation, and formulation of management guidelines for patients with HCC.

Materials and Methods

STUDY POPULATION

Patients were recruited from an ongoing HCC registry database that has been prospectively enrolling patients seen in our department who had been diagnosed with HCC since 1988. Our institution is the largest not-for-profit tertiary care teaching hospital in Singapore, consisting of 1,600 beds and over 30 clinical disciplines. As such, we are one of the major national referral centers for subspecialty care, and a considerable number of patients with HCC are seen in our institution. However, other hospitals in Singapore also treat HCC. Similarly, oncologists in our institution also manage patients with advanced HCC, but as the majority of these patients also have a background of liver cirrhosis, they would concurrently be under the care of our department. HCC was diagnosed based on conventional diagnostic criteria according to the time period.[13-15] These criteria included histology and diagnostic radiology imaging techniques, such as hepatic angiography and positive lipiodol angiography, prior to 1990 and dynamic contrast-enhanced radiology modalities thereafter.

STUDY DESIGN

A retrospective analysis of patients with HCC diagnosed between January 1, 1988, and April 30, 2016, was performed. Demographic and clinical data were collected. The etiology of HCC was defined as hepatitis B related if hepatitis B surface antigen (HBsAg)

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TABLE 1. DISTRIBUTION OF ETIOLOGY AMONG PATIENTS WITH HCC

Etiology	Overall (%)	C1 n = 764 (%)	C2 n = 637 (%)	*P* Value
Hepatitis B	1001 (72.7)	572 (76.5)	429 (68.2)	<0.001
Hepatitis C	56 (4.1)	23 (3.1)	33 (5.2)	0.054
Hepatitis B and C co-infection	55 (4.0)	45 (6.0)	10 (1.6)	<0.001
Alcohol	55 (4.0)	13 (1.7)	42 (6.7)	<0.001
Cryptogenic	207 (15.0)	95 (12.7)	112 (17.8)	0.010
Primary biliary cholangitis	2 (0.15)	0	2 (0.32)	--
Autoimmune hepatitis	1 (0.07)	0	1 (0.16)	--
Viral	1112 (80.8)	640 (85.6)	472 (75.0)	<0.001
Nonviral	264 (19.2)	108 (14.4)	157 (25.0)	

serology was positive, hepatitis C related if immunoglobulin (Ig)G antibody serology for hepatitis C was positive, and alcohol related if patients had a daily consumption of more than 60 g of alcohol for 10 years or more. Alcohol consumption was assessed by trained medical staff interviewers using a standardized questionnaire ascertaining the type of alcoholic beverage consumed, strength of alcoholic beverage (percentage alcohol), number of drinks, frequency of consumption (daily/weekly/monthly/hardly ever/never), and duration of alcoholic consumption. If deemed clinically indicated, additional tests, such as antinuclear antibody, serum ceruloplasmin, and anti-liver antibodies, were performed to elucidate the underlying liver disease. Cases were considered cryptogenic HCC if viral hepatitis B/C serology was negative, there was no documented excessive alcohol intake, and other causes of chronic liver disease had been excluded. Child-Pugh class and functional performance status by Eastern Cooperative Oncology Group (ECOG) grading were recorded as was the manner in which HCC was diagnosed, viz., while under routine surveillance or otherwise. Under our surveillance practices, patients received a regular ultrasound abdominal scan and serum alpha-fetoprotein on a 6 monthly schedule or more frequently as deemed necessary by the patient's physician. Staging of HCC was assessed using the Barcelona Clinic Liver Cancer (BCLC) classification.[16] Type of treatment provided for the HCC was categorized into surgical curative, local ablative, systemic chemotherapy, and best supportive care. Curative therapies were defined by surgical resection, liver transplantation, and radio frequency ablation (RFA) of HCC less than 3 cm. All the current standard of care treatment modalities of HCC were available in our hospital; hence, our hospital offers all possible standard of care treatment approaches to optimize patient outcomes. Details of patient survival were computed using death data from the Singapore National Registry of Births and Deaths. As the law mandates compulsory reporting to the National Registry of Births and Deaths only for deaths of Singapore citizens and as the survival census was performed on October 31, 2015, survival analysis was restricted to a cohort of 1,270 (90.6% of total cohort) patients who were Singapore citizens with HCC diagnosed before the census date of October 31, 2015. Clinical characteristics, treatment modalities, and survival outcomes were compared between two time periods: cohort 1 spanning 1988-2002 (C1) and cohort 2 spanning 2003-2016 (C2). The study was approved by the institutional review board of Singapore General Hospital.

STUDY ANALYSIS

Descriptive statistics were computed for all variables, including frequency with percentages (%) for categorical variables and mean with SD for continuous variables. Differences in demographic, clinical, and laboratory data were explored between patients in C1 and C2, using the Student *t* test and chi-square testing for continuous and categorical variables, respectively. Survival analysis was performed using Kaplan-Meier with log-rank testing for significance differences between groups. All statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY). All *P* values were two-sided with $P < 0.05$ considered statistically significant.

Results

There were 1,401 patients included in the study, of which 764 patients and 637 patients were in C1 and C2, respectively. Distribution of the etiology of HCC across the two time periods is illustrated in Table 1. Hepatitis B remained the dominant etiology of HCC in both eras; however, there was a significant decline in hepatitis B-related HCC between C1 and C2. On the

TABLE 2. BASELINE PATIENT CHARACTERISTICS

Characteristics		C1 (n = 764)	C2 (n = 637)	*P* Value
Age at diagnosis (years)	Overall	60.1 ± 13.0	63.5 ± 10.9	<0.001
mean ± SD	Hep B	58.0 ± 13.0	61.9 ± 10.9	<0.001
	Hep C	67.0 ± 11.1	60.5 ± 10.4	0.018
	Hep B and C co-infection	66.1 ± 10.0	65.8 ± 12.8	0.861
	Alcohol	62.6 ± 8.3	63.1 ± 8.9	0.897
	Cryptogenic	65.9 ± 11.8	69.2 ± 8.7	0.062
	Viral	58.9 ± 13.0	61.9 ± 10.9	0.001
	Nonviral	65.5 ± 11.4	67.7 ± 9.2	0.194
Male (%)		641 (83.9)	508 (79.7)	0.044
Male:female ratio		5.2:1	3.9:1	
Chinese (%)		686 (89.8)	561 (88.1)	0.305
ECOG score	0	150 (20.4)	354 (62.1)	<0.001
	1, 2	518 (70.3)	173 (30.4)	<0.001
	3, 4	69 (9.4)	43 (7.5)	0.260
Child-Pugh class	A	339 (48.6)	315 (52.9)	0.123
	B	254 (36.4)	205 (34.4)	0.457
	C	104 (14.9)	75 (12.6)	0.230
Child-Pugh score	Median	7.00	6.00	0.040

other hand, there was a significant increase in the number of patients with nonviral HCC from C1 to C2. The frequency of alcohol-related HCC increased from 1.7% in C1 to 6.7% in C2, while that of cryptogenic HCC increased from 12.7% to 17.8%, respectively.

The mean age at diagnosis of HCC was significantly older in C2 compared to C1 (63.5 versus 60.1 years, respectively; $P < 0.001$) (Table 2). Patients with hepatitis B-related HCC were diagnosed at an older age in the later (C2) cohort compared to the earlier (C1) cohort, whereas the mean age for the other etiologies did not change (alcohol, cryptogenic) or had decreased (hepatitis C).

Interestingly, there was a slight but significant reduction in the proportion of male patients with HCC in C2 compared to C1 (79.7% versus 83.9%, respectively; $P < 0.05$). Patients with HCC in C2 had better physical performance status, with 62.1% having ECOG 0 compared to only 20.4% in C1. There was no significant difference in severity of liver disease between the two temporal cohorts as reflected by the similar distribution of Child-Pugh class between C1 and C2.

The mode of diagnosis of HCC, HCC extent (BCLC stage), and treatment provided between C1 and C2 are described in Table 3. There was a significant increase in HCC diagnosed via surveillance in C2 compared to C1 (39.2% versus 11.3%, respectively; $P < 0.001$). Patients with HCC in C2 had better ECOG scores and BCLC stages. Correspondingly, significantly more patients in C2 were amenable to curative and loco-ablative treatment modalities. This translated to a significantly improved median survival in C2 compared to C1 (18.6 versus 3.8 months, respectively; $P < 0.001$) (Fig. 1). When survival analysis in C2 was stratified according to treatment modality, patients who received curative therapies had a median survival of 60.2 months as opposed to a significantly lower median survival of 9.4 months ($P < 0.001$) for those who did not receive curative therapies. Further stratification of treatment modality into liver

TABLE 3. HCC CHARACTERISTICS

			C1 (n = 764) (%)	C2 (n = 637) (%)	*P* Value
Mode of diagnosis	Surveillance		86 (11.3)	250 (39.2)	<0.001
	Nonsurveillance		678 (88.7)	387 (60.8)	
BCLC	0		8 (1.2)	73 (13.1)	<0.001
	A		40 (6.2)	147 (26.4)	<0.001
	B		47 (7.3)	114 (20.5)	<0.001
	C		453 (70.3)	156 (28.0)	<0.001
	D		96 (14.9)	67 (12.1)	0.146
Treatment	Curative		91 (13.0)	282 (61.4)	<0.001
	Other therapy	Loco-ablative	83 (11.8)	83 (18.1)	<0.003
		Chemotherapy	104 (14.8)	30 (6.5)	<0.001
	Supportive		424 (60.4)	64 (13.9)	<0.001

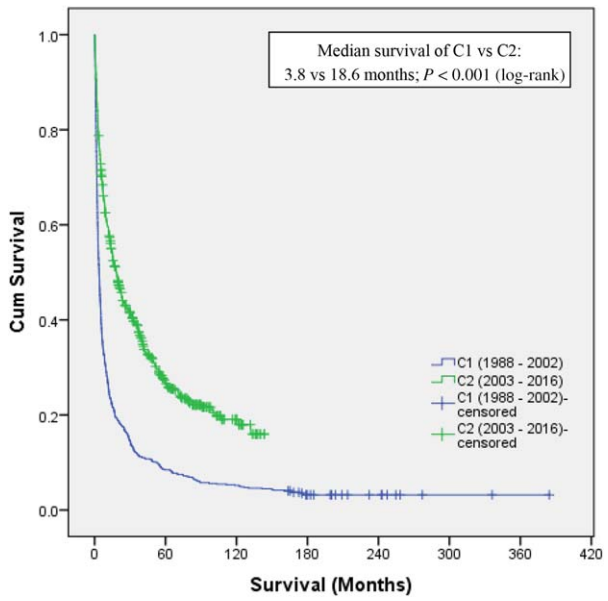

FIG. 1. Kaplan-Meier survival comparison between C1 and C2.

transplant, hepatic resection, RFA, loco-ablative, and supportive care demonstrated median survivals of 73.5, 50.9, 18.8, 3.6, and 5.2 months, respectively. In C1, similar survival trends were also noted, with patients given curative therapies having significantly better median survival compared to noncurative modalities (70.1 versus 3.0 months, respectively; $P < 0.001$).

Discussion

Our study highlights several striking evolutionary changes of HCC in Singapore over the last 3 decades in both patient and tumor characteristics. In terms of etiology, the dominance of CHB is on the decline while heralding a trend of increasing nonviral-related HCC. Hepatitis B remains endemic in many parts of Asia and strongly correlates to the risk of HCC development.[17,18] Fortunately, with the development and successful implementation of nationwide hepatitis B immunization programs, a significant decline in seroprevalence of HBsAg and CHB has been observed in many countries, including Singapore. Singapore began a nationwide hepatitis B immunization program in 1987, and this has now had an impact on the seroprevalence rates in the younger population where HBsAg prevalence dropped from 4.1% to 1.1% among young adults below 30 years of age.[9] Along similar lines, a separate study conducted between 2008 to 2010 demonstrated that HBsAg prevalence was only 0.3% in subjects less than 17 years of age.[19] Hence, a decrease in CHB-related HCC rates can be expected with a successful reduction in CHB infection incidence. This was demonstrated in Taiwan, where a hepatitis B virus (HBV) immunization program started in 1984 was followed by a significant decline in HCC incidence among Taiwanese children.[20] A subsequent follow-up report of the same cohort 12 years later showed that the significant lowering of the HCC incidence rate had extended beyond childhood into adolescence.[21] A separate explanation to account for the decline of CHB-related HCC is the positive impact of HBV treatment. Both interferon and nucleotide analogue-based regimes have been shown to reduce the risk of HCC.[22-25] In addition, long-term therapy with nucleotide analogues has been associated with the regression of fibrosis and cirrhosis, thus negating one of the important pathways of oncogenesis.[26]

Juxtaposed against the decline of CHB-related HCC is the emergence of nonviral-related HCC. An upsurge of alcoholic-related HCC was seen across the 2 eras, reflecting an increase in alcoholic liver disease. Evidence for this is suggested by the rising prevalence of frequent (from 4.5% to 7.5%), regular (from 2.9% to 3.1%), and binge drinking (from 5.1% to 10.0%) between 1992 and 2004, which in turn is attributed to the rapid economic transition and shift toward an evolving drinking culture seen in Singapore over the last few decades.[27] Along similar lines, the incidence of cryptogenic HCC has also been increasing across the 2 eras. Cryptogenic HCC often represents "burnt out" nonalcoholic steatohepatitis (NASH), where a significant number of these patients have the clinical phenotype consistent with NASH, such as higher prevalence of metabolic risk factors.[28,29] Socioeconomic changes seen with rapid modernization, increasing affluence, and a shift to a more sedentary lifestyle and obesogenic dietary patterns predispose to NASH.[11,30] In our local context, the prevalence of NASH risk factors, such as obesity, increased from 6% in 1998 to 10.8% in 2010, while diabetes mellitus increased from 9% in 1998 to 11.3% in 2010, which intuitively would translate into an increasing prominence of NASH and consequently NASH-related (i.e., cryptogenic) HCC.[10] This can also be extrapolated to many other countries that are afflicted by the burgeoning obesity and diabetes epidemic.[31-33]

An interesting evolving patient characteristic is the "aging" of the patient with HCC; the mean age at which patients develop HCC has increased over time.

This is consistent with current literature reported in both Western and Asian studies.[34-36] In our study, this aging effect was observed only in patients with CHB-related HCC. One postulation is that nucleotide analogue therapy slows rather than prevents hepatocarcinogenesis, particularly in the context of preexisting advanced fibrosis/cirrhosis.[37,38] Alternatively, increased use of hepatitis B vaccination and CHB treatment by the younger population has reduced the incidence of HCC in the younger age groups; as this does not benefit the patients with CHB from the prevaccination or treatment eras, the mean age of HCC development is shifted to an older age. This has been shown by Hung and colleagues[39] in a study in which elderly patients (>65 years) with HCC comprised 49.1% of their cohort and upward trends of HCC incidence were observed only in elderly patients. Similarly, Seto et al.[40] have recently shown that the decline in age-adjusted HCC incidence in age groups <65 years old in Hong Kong is likely due to higher use of nucleoside analogues by the younger population. The clinical implication of this aging effect is that adequate resources and workflow must be tailored to screen, diagnose, and treat HCC in a more geriatric population.

Another interesting but less described trend is the evolving sex distribution. While male preponderance remains across the 2 eras, there was a significant decline in the proportion of male patients in the later era, such that the male to female ratio decreased from 5.2:1 to 3.9:1 across the 2 eras. The worldwide progressive sex disparity in HCC incidence is not well understood.[2,3] As there are significantly fewer patients with HBV-related HCC in C2 compared to C1, one possible explanation for the greater reduction of HCC in the male compared to the female population in C2 is the greater impact of HBV treatment in male patients compared to female patients. It has been shown that due to differential sex hormone and androgen receptor activity, HBV replication is approximately twice as efficient in male mice, which is one reason for the sex discrepancy of HBV-related HCC.[41] We postulate that the advent of highly effective nucleotide/nucleoside analogue therapy for HBV in C2 has resulted in better viremic control of HBV overall and consequently reduced HBV-related hepatocarcinogenesis. However, this may be more distinctly appreciated in male patients in the context of interaction between sex hormone/androgen receptor activity and reduced HBV viremia. This translated into a greater decrease in HBV-related HCC seen in male patients compared to female patients in C2. As the majority of HCC cases are still HBV related in C2, this has in turn resulted in a significant fall in the male to female ratio of HCC in C2 compared to C1.

With regards to tumor characteristics over the last 3 decades, our study demonstrated that a significantly greater proportion of HCC cases was diagnosed via surveillance programs in the later era. Hence, as expected, patients in the later era also had better performance status (ECOG) and earlier tumor stage (BCLC). These translated to more patients in the later era being eligible for active HCC therapy, with a significant improvement in survival over the earlier era. These results are consistent with several previous studies exploring evolutionary temporal trends in HCC. The role of HCC surveillance in chronic liver disease has become well established over the years, with benefits reported in several studies.[42-44] Similarly, a significant improvement in diagnostic modalities, such as dynamic computerized tomography, contrast-enhanced magnetic resonance imaging, and ultrasound, has also played an important role in detecting HCC earlier.[35] Intuitively, identifying asymptomatic patients with HCC earlier would translate to patients being diagnosed at initial stages of disease, a term coined stage migration. Certainly, this was evident in our study where there were more patients with HCC in early BCLC stages (0, A, and B) in the later era. This has a tremendous impact on eligibility for treatment, allowing more patients to receive curative and effective palliative therapy, such as surgical resections and local ablative treatment. As illustrated in our study, more patients with HCC underwent curative or loco-ablative therapy with fewer patients receiving supportive care in the later era. Liver transplantation was considered a curative treatment modality but may not have had a significant impact on outcomes as our hospital liver transplant program was only established in 2004 and still remains a low-volume center due to low organ supply. Undeniably, better surgical techniques, improved peri-operative care, and the introduction of new effective treatment options, such as RFA and transhepatic arterial chemoembolization, have also contributed to improved outcomes. As a result, patient survival significantly increased in the later era, which is a reflection of the various factors mentioned above. Other studies have also observed similar trends in survival.[34,37,45,46] Despite demonstrating a significant improvement of survival over time, the median survival of 18.6 months in the later era still seems rather low. Golabi and colleagues[47] looked at 2-year survival rates of patients with HCC in the Surveillance,

Epidemiology and End Results database between 2001 and 2009 and found that 75.4% of the patients had died within 2 years; further subanalysis showed mortality within 2 years for those who underwent liver transplant, hepatic resection, and nonsurgical treatment to be 29.1%, 43.7%, and 85.3%, respectively. It is likely that the high mortality rate of those patients in the nonsurgical treatment group greatly impacted the overall survival rates in their study. We found similar circumstances in our study, with the noncurative treatment group dramatically pushing our overall median survival down.

This study has several strengths. The data were extracted from a large and robust HCC registry that spanned 3 decades, allowing sufficient time to decipher evolutionary trends. Furthermore, our survival data were accurate and comprehensive because the survival census was based on our National Registry of Births and Deaths and the reporting of all deaths is mandated by law. Some limitations of our study include the possible subjective nature of assessment of alcohol consumption based on patient reporting, which we have tried to minimize with our standardized questionnaire. We also acknowledge the inability to retrospectively record some data, such as metabolic risk factors, in the patients enrolled early on and a possible biased patient population as we are a referral center for HCC and viral hepatitis in the country. Nevertheless, our study provides detailed insight into the temporal trends of HCC in Singapore, a country that has undergone rapid socioeconomic development over the time period of the study.

In conclusion, there have been significant changes in the epidemiology and management of HCC during the last 3 decades. These include changing etiologies, better use of surveillance programs to diagnose earlier stage HCC, and translating to improved survival. These data can be further used to forecast future trends and guide management strategies to reduce the incidence and disease burden of HCC.

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