RESEARCH ARTICLE

Characteristics of Liver Cancer at Khmer-Soviet Friendship Hospital in Phnom Penh, Cambodia

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Abstract

Background: Hepatocellular carcinoma (HCC) is one of the most frequent cancers in South East Asian countries including Cambodia, where prevalence of chronic carriers of hepatitis B and C virus (HBV and HCV) is reported to be very high. We reviewed HCC cases admitted to a cancer hospital in Phnom Penh, which is the only one hospital for cancer treatment and care in Cambodia during the study period. Materials and Methods: Information was collected from medical records of 281 cases (210 males and 71 females) diagnosed as primary HCC from 2006 to 2011. Results: The subjects were 7-81 years old with a median age of 53 years. Hypochondriac pain was the most common complained symptom (74%). One third of the cases presented with jaundice. Nearly half had ascites at their first visit. One third had liver cirrhosis. Nearly three fourths of the cases presented with tumor sized more than 50 mm in diameter, and in almost all cases (97.4%) the size was more than 20 mm. Among 209 subjects tested, hepatitis virus carriers were 75.6%; 46.4% for HBV only, 21.5% for HCV only, and 7.7% for both viral infections. Median age of patients with HBV was about ten years younger than those with HCV. Conclusions: This study revealed the characteristics of HCC cases in Cambodia, although there were several limitations. Most HCC cases were infected with HBV and/or HCV, and diagnosed at late stages with complications. This implicated that public health intervention to prevent HBV and HCV infection is of high priority.

Keywords: Hepatocellular carcinoma - hepatitis B virus - hepatitis C virus - Cambodia

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Introduction

In ASEAN countries, hepatocellular carcinoma (HCC) is the second most frequent cancer both in incidence and mortality. The incidence and mortality per 100,000 population were found to be 33.8 and 32.3 in Laos PDR, 29.7 and 25.4 in Thailand, 29.3 and 29.2 in Vietnam, 5.2 and 5.4 in Brunei, 5.7 and 5.4 in Malaysia, and 6.7 and 6.6 in Indonesia, respectively (Kimman et al., 2012). In the neighboring countries of Cambodia (Laos, Thailand, and Vietnam), HCC is the leading cancer (Srivatanakul, 2001; Ngoan et al., 2007; Nguyen et al., 2011).

Cambodia does not have either a cancer registry nor correct mortality statistics, although GLOBOCAN program/IARC (International Agency for Research on Cancer) estimated the incidence and mortality in Cambodia based on closer countries and Cambodian hospital statistics (Eav et al., 2012). According to the estimates, cancer incidence per 100,000 in Cambodia was approximately 153 for males and 123 for females. In males, liver cancer was the most common cancer (20% of all male cancers), followed by lung cancer (18%), gastric cancer (11%), colorectal cancer (9%), and lymphoma (6%), while cancer of the cervix uteri ranked the first (25% of all female cancers), followed by breast cancer (19%), lung cancer (7%) and liver cancer (6%) in females (Eav et al., 2012). Liver cancer was also the leading cause of death among Cambodian immigrants to France between 1979 and 1985 (Boucharrdy et al., 1994).

The causes for the high occurrence of HCC in developing countries were chronic infection of hepatitis B virus (HBV) and hepatitis C virus (HCV), as well as dietary exposure to a fungal toxin-aflatoxin. HBV chronic infection was more than 8% of the population, and about 25% of the infected people were estimated to develop HCC (Kew, 2010). Many studies reported the prevalence of hepatitis infection among Cambodians. The reported prevalence varied largely among different geographical areas and different periods of survey; 7.7% to 11.8% for HBV and 2.3% to 14.7% for HCV (Thuring et al., 1993; Sarmati et al., 2003; Buchy et al., 2004; Caruana, 2005; Ha et al., 2009; Sann et al., 2009; Sa-Nguanmoo, 2010; Akkarathamrongsin et al., 2011; Kowdley et al., 2012). Among those with elevated serum levels of alanine

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aminotransferase (ALT) and aspartate aminotransferase (AST) measured at Pasteur Institute Phnom Penh, 41% and 39% were found to be positive for HBV antigen and HCV antibody, respectively (Buchy et al., 2004).

HCC has a shorter survival time than other cancers, especially for patients in low-income countries. The reasons for the shorter survival time are late diagnosis, lack of specialized medical professionals, and limited resources for diagnosis and treatments. Financial and logistical barriers influence poor prognosis (Kew, 2012).

To the best of our knowledge, no study has been conducted on clinical features of HCC in Cambodia. This study aimed to reveal the demographic and clinical characteristics of HCC patients in Cambodia, based on medical records available at a cancer hospital.

Materials and Methods

After Khmer Rouge Regime and civil war, Cambodia reopened a cancer treatment facility, "Khmer-Soviet Friendship Hospital" (KSFH), in Phnom Penh, 2003. This cancer facility was the only one cancer treatment and care facility in Cambodia during this study period.

Subjects were 281 patients admitted to KSFH from January 2006 to December 2011 and diagnosed as primary HCC. Their demographic information, risk factors, clinical profile, hematological and biochemistry tests, and medical imaging records were extracted from medical records. The biopsy was rarely performed, so that the pathological diagnosis was not done in most cases. The laboratory and medical imaging reports were not available for some cases. Many patients were discharged from hospital with pain killer because of poverty and hopelessness. Accordingly, the information on their prognosis and survival was not available. The criteria for HCC diagnosis were mainly based on clinical findings and tumor markers. Although reports of imaging tests were used for the diagnosis, the hypervascularity in the arterial phase and washout in the portal equilibrium phase on dynamic computerized tomography (CT) scanner or dynamic magnetic resonance imaging (MRI) was not available from the medical records (Kudo et al., 2011). Majority of imaging diagnosis were based on ultrasound detection.

The precise information of alcohol consumption was not available, but heavy alcohol drinking was subjectively reported and recorded in their medical chart. Aflatoxin or dioxin (herbicide) agents (Villar et al., 2012; Jun et al., 2014), cryptogenic cirrhosis (Somboon et al., 2014) as well as liver fluke, Opisthorchis viverrini (Ngoan et al., 2001), were not recorded. Difference in ratio or proportion was examined by a Pearson chi-square test. The data were analyzed by SPSS version 20 software. This study was approved by National Ethics Committee for Health Research (NECHR) of the Cambodian Ministry of Health on July 2, 2012.

Results

The demographic characteristics of HCC patients and their underlying factors are presented in Figure 1. The overall mean and median age were the same (53 years), and the age range was 7 to 81 years. The male and female ratio of the HCC subjects was 3.0. Those aged 40 to 69 years were the majority of the subjects (74.4%). Of 281 patients, 72% patients came from provinces, and the rest came from the capital city.

Two hundreds and nine subjects were tested for serology of hepatitis B surface antigen and hepatitis C antibody. The laboratory tests confirmed that 75.6% (158/209) had HBV and/or HCV infection; 46.4% (97/209) had HBV only, 21.5% (45/209) had HCV only and 7.7% (16/209) for both. The median age of subjects with HBV positive and HCV negative was more than 10 years younger than that of subjects with HBV negative and HCV positive in both sexes; the former was 48 years in males and 50 in females, while the latter was 60 years and 65 years, respectively. The youngest patient was a man aged 25 years among those with HBV positive and a woman aged 34 years among those with HCV positive. The testing of HBV and HCV was not available for a girl aged 7 years. Male to female ratio was 4.4 (79/18) for those with HBV positive and HCV negative, 4.0 (36/9) for those with HBV negative and HCV positive, 4.3 (13/3) for those with both positive, and 1.8 (33/18) for those with both negative. The male to female ratio of both negative (1.8, 33/18) was significantly (p=0.016) lower than of

Table 1. Clinical Symptoms and Signs of Hepatocellular Carcinoma Patients

Symptons/signs	Overall		HBsAg(+) HCVAb(-)		HBsAg(-) HCVAb(+)		HBsAg(+) HCVAb(+)		HBsAg(-) HCVAb(-)	
	n	%	n	%	n	%	N	%	n	%
Total	281	100	97	100	45	100	16	100	51	100
Weakness	140	49.8	46	47.4	25	55.6	7	43.8	28	54.9
Anorexia	94	33.5	32	33	14	31.1	7	43.8	13	25.5
Abdominal pain	208	74	71	73.2	31	68.9	12	75	40	78.4
Weight loss	74	26.3	24	24.7	12	26.7	5	31.3	10	19.6
Ascites	126	44.8	46	47.4	24	53.3	8	50	18	35.3
Fever	27	9.6	9	9.3	6	13.3	1	6.3	3	5.9
Jaundice	85	30.2	37	38.1	11	24.4	7	43.8	14	27.5
GI bleeding	15	5.3	6	6.2	1	2.2	1	6.3	3	5.9
Hepatomegaly	194	69	68	70.1	31	68.9	10	62.5	41	80.4
Pallor	40	14.2	17	17.5	9	20	5	31.3	10	19.6
Edema	52	18.5	17	17.5	11	24.4	4	25	12	23.5
Cirrhosis	86	30.6	34	35.1	20	44.4	7	43.8	5	9.8
Splenomegaly	58	20.6	21	21.6	12	26.7	4	25	9	17.6

Table 2. Serum Findings at Diagnosis for Hepatocellular Carcinoma Patients

Parameter	Overall Mean (SD)	HBs Ag(+) HCV Ab(-) Mean (SD)	HBs Ag(-) HCV Ab(+) Mean (SD)	HBs Ag(+) HCV Ab(+) Mean (SD)	HBs Ag (-) HCV Ab (-) Mean (SD)	p value*
Hemoglobin (g/dl)	11.2 (21.5)	16.0 (23.0)	13.2 (15.0)	10.6 (1.3)	15.7 (20.2)	0.4817
Glycemia (mg/dl)	105.8 (46.8)	102.0 (53.0)	112.2 (56.1)	159.2 (99.8)	92.0 (52.6)	0.4177
Total bilirubin (IU/l)	5.9 (12.5)	7.0 (16.0)	5.3 (8.6)	4.2 (4.7)	3.3 (4.6)	0.5848
Direct bilirubin (IU/l)	3.8 (10.2)	4.0 (11.0)	1.0 (6.0)	2.7 (4.0)	3.7 (12.7)	0.16
PTI (%)	61.9 (19.9)	61.0 (20.0)	53.8 (20.7)	52.9 (23.5)	71.2 (19.3)	0.2151
AFP (ng/dl) n=171	6,011.0 (27,130.0)	7,264.0 (28,808.0)	6,287.9 (30,740.4)	1,125.9 (1,219.0)	360.0 (642.8)	0.8897
≥400 ng/dl (n, %)	89 (52.0)	40 (60.6)	18 (69.2)	6 (54.5)	8 (22.2)	
<400 ng/dl (n, %)	82 (48.0)	26 (39.4)	8 (30.8)	5 (45.5)	28 (77.8)	
Albumin (g/dl); n=106	3.8 (1.1)	3.9 (12.7)	33.5 (12.7)	35.1 (9.9)	40.8 (17.6)	<0.0001
<3.0 g/dl (n, %)	24 (22.6)	6 (16.7)	9 (40.9)	4(40.0)	3 (18.8)	
≥3.0 g/dl (n, %)	82 (77.4)	30 (83.3)	13 (59.1)	6(60.0)	13 (81.2)	
AST (IU/l) n=216	132.5 (183.6)	272.0 (1,020.0)	342.0 (1,438.2)	966.0 (2,653.1)	93.0 (88.2)	0.795
>2 x ULN (n, %)	177 (81.9)	76 (90.5)	29 (82.9)	12 (85.7)	32 (69.6)	
ALT (IU/l) n=216	99.2 (85.5)	112.0 (89)	96.9 (84.0)	115.2 (103.1)	87.3 (88.2)	0.3868
>2 x ULN (n, %)	173 (80.1)	74 (88.1)	27 (77.1)	13 (92.9)	31 (67.4)	

* p value of HBV Ag (+) HCV Ab(-) and HBV Ag(-) HCV Ab(+); AFP: alpha-fetoprotein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, PTI: prothrombin time index and ULN: upper limit of normal

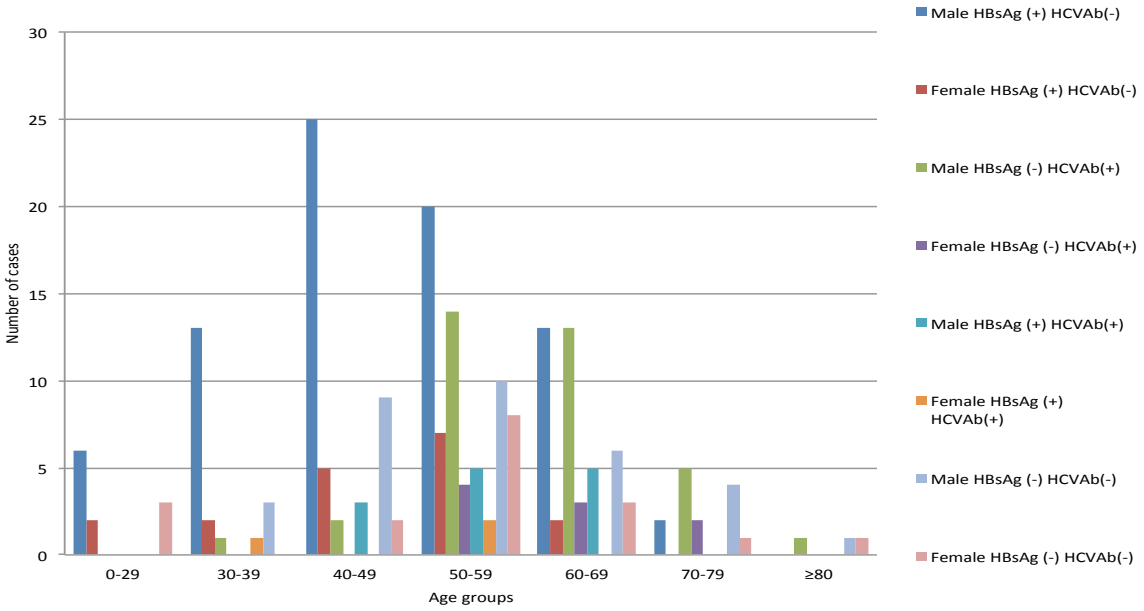

Figure 1. Age Distribution According to Sex and Hepatitis Viral Infection

those of HBV and/or HCV positive (4.2, 128/30). Heavy alcohol drinking was subjectively reported by 33.1% (93/281) studied subjects, although the quantity of alcohol consumed by patients was not recorded.

As shown in Table 1, abdominal pain was the most common symptom of HCC subjects (74.0%), followed by weakness (49.8%) and ascites (44.8%). Hepatomegaly was the most common sign (69.0%). Of total, 30.6% of the patients had liver cirrhosis. Liver cirrhosis was significantly more common among patients who were HBV/HCV positive than that among patients with both negative; 38.6% (61/158) and 9.8% (5/51), respectively (p<0.001).

Table 2 shows serum findings at diagnosis for hepatocellular carcinoma patients. The data on alpha-fetoprotein (AFP) level were available for 171 HCC cases, of whom 52.0% (89/171) were 400 ng/dl or higher. The median serum AFP level was 453ng/dl, ranging from 0.40 to 219,000 ng/dl. Patients with aspartate aminotransferase (AST) more than two times higher than the normal level were 81.9%, and the corresponding percentage for alanine aminotransferase (ALT) was 80.1%. Data on albumin were available for 106 patients, of whom 22.6% were less than 3.0 g/dl. Among 135 cases with bilirubin records, the median was 2 IU/l (range, 0.56-124 IU/l) for total bilirubin and 0.8 UI/l (range, 0.14-84 IU/l) for direct bilirubin. Median of prothrombin time rate as 61.5 (range 9-100), and median of hemoglobin was 11.3 g/dl (range 4.9-17.6g/dl).

Medical imaging was performed by ultrasound (US) in 195 cases and by CT scan in 37 cases. Among the 232 subjects tested by either US or CT, lesions were found in the right lobe for 54.3%, in the left lobe for 17.7%, and in both lobes for 28.0%. The size in lesion was >50 mm in 73.3% of cases, 20-49 mm in 24.1% of cases, and <20 mm in 2.6% of cases. More than half of cases (55.2%) presented two or more lesions, while the other 44.8% had developed a single tumor. Among 195

patients with US test, 23.1% had hypoechoic legion(s), 51.8% had hypereechoic lesion(s), and 25.1% had heterogenous lesions. The CT scanning found quite similar characteristics of the lesions-hypodensity was found in 73.0% of the cases; hyperdensity was found in 2.7% and mixed density was found in 24.3% of the subjects.

Discussion

This was the first study on features of HCC at diagnosis in Cambodia. It provided important information on demographic, clinical, and risk factors of primary HCC. In this study, clinically diagnosed HCC cases were retrospectively selected from the medical records. The main indicators used for the diagnosis were 1) elevated serum AFP and 2) liver lesions detected by a US test or a CT scan. Chronic HBV and HBC infection and cirrhosis were also used for supplemental indicators for the diagnosis of HCC.

Although the information for the precise staging of HCC was not available in the present study, the majority of subjects were considered to be at a late stage. The indicators of the late stages included hepatomegaly (69.0%), ascites (44.8%), jaundice (30.2%), liver cirrhosis (30.6%), edema (18.5%), and large size of tumors (73.3% for 5 cm or larger).

In this study, HBV and HCV infections were identified for 75.6% of HCC patients; 46.4% with HBV only, 21.5% with HCV only, and 7.7% with co-infection of HBV and HCV. It was quite similar to a study of North-east Peninsular Malaysia in which HBV was recorded in 57.6% but less HCV, 2.4%, of HCC study (Norsa'adah et al., 2013) and in some parts of Thailand where HBV was identified between 40-65% of HCC cases, and HCV was recognized in 16-17% of cases (Samboon et al., 2014; Galy et al., 2011; Tangkijvanich et al., 2003). In Vietnam, a study found that HBV was detected in 60.5% of HCC cases and HCV was discovered in 2.6% of the cases (Ding et al., 2003). In Asia Pacific regions (Cambodia, China, Cook Islands, Federated States of Micronesia, Fiji, Kiribati, Laos, Malaysia, Marshall Islands, Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, South Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam) where HBV was reported as a risk factor of 53% of HCC cases and HCV was reported in 25% of the cases. Globally, HBV and HCV accounted for 65% and 78% of the contributing causes of HCC, respectively (Perz et al., 2006). It is also important to note that 24.5% of cases were both HBV and HCV negative in this study. There should be the risk factors other than chronic hepatitis infection, but the information on aflatoxin, Opisthorchis viverrini, and chemical agents such as herbicide was not available.

In this hospital-based case-series study, the subjects aged 40 to 69 years were the most commonly suffered from HCC in both sexes. The overall mean age of the study subjects was 53 years, which was quite similar to 53.8 in the study on HCC cases in northern Thailand (Leerapun et al., 2013). The mean age of the HBV-positive HCC cases were 10 years lower than those with HCV positive (48.0 versus 61.4 years), which was similar to a study in Japan (Tanizaki et al., 1997). A study conducted by the Bellevue Hospital Center in New York also found an 8-year discrepancy (Hiotis et al., 2012). The male-to-female ratio was 3.0 (210/71) in this study. The ratio was higher among those with HBV and/or HCV positive than among those with both HBV/HCV negative. The reason remained to be further investigated.

In poor resource countries like Cambodia, measures to reduce the burden of preventable diseases including HCC are important. Cambodia has introduced hepatitis B vaccination for children into its National Program of Immunization in 2002. This intervention has been preventing Cambodian children from chronic hepatitis infection by immunizing them against hepatitis B infection. However, health education to reduce or cut transmission routes is yet to be scaled up and expanded. The measures are very critical for Cambodia to prevent hepatitis transmission, because medical services for this disease are expensive. The secondary prevention might be useful to improve their prognosis, but the screening and subsequent treatments are also heavy burdens to meet the increasing demands. This study provided the information on HCC patients in Cambodia, which could be used for the reduction of the socioeconomic burdens due to HCC (Jan et al., 2012).

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