The Influence of Medical Subspecialty on the Adherence to Hepatocellular Carcinoma Surveillance in Patients with Chronic Hepatitis B

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ABSTRACT

Objective: This study aimed to determine the adherence rate of HCC surveillance in CHB patients at the largest tertiary hospital in Southern Thailand and identify patient and physician factors that influence it.

Materials and Methods: This retrospective cohort study included patients with CHB who were followed up for more than 1 year between 2011 and 2019 at a tertiary care hospital in Thailand. Patients diagnosed with HCC within 6 months of their first visit were excluded. The rate of adherence with HCC surveillance was calculated using percentage of time up-to-date with HCC surveillance (PTUDS).

Results: The mean age of 531 eligible patients at the time HCC surveillance started was 55.5 ± 9.26 years. The most common indications for surveillance were male over 40 years of age (41.2%), female over 50 years of age (28.9%), and cirrhosis (22.6%). The median PTUDS was 70.6% (interquartile range 55.1 – 81.4%). The highest PTUDS was for cirrhosis (74.0%). For physicians' subspecialties, the median PTUDS was 71.8% for gastroenterologists (IQR 58.3 – 81.6%) and 41.7% for internists (IQR 31.4 – 65.8%). Factors associated with increased PTUDS by multivariable analysis were having ≥2 clinical visits per year (±18.4%, p<0.001), civil servant reimbursement (±8.81%, p=0.001), cirrhosis (±6.06%, p=0.003), and being follow-up by gastroenterologists (±20.4%, p<0.001).

Conclusion: The adherence with surveillance program in patients with CHB being followed up at a tertiary care setting in Thailand was good. This finding underscores the importance of education regarding indications for HCC surveillance, particularly in patients without cirrhosis.

Keywords: Hepatocellular carcinoma; surveillance; hepatitis B; adherence; compliance (Siriraj Med J 2024; 76: 216-224)

INTRODUCTION

Chronic hepatitis B (CHB) infection is a public health concern worldwide. In 2015, there were approximately 275 million people living with CHB.[1] In Thailand, approximately 2.9 to 5.1% of the population, or up to 3 million people, had CHB.[2,3] CHB significantly increases the risk of developing hepatocellular carcinoma (HCC) and accounts for 32% of all causes of HCC worldwide and 50% in Thailand.[4,5]

HCC is the second most common cause of cancer-related mortality worldwide.[4] The American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), and Asian Pacific Association for the Study of the Liver (APASL) recommend that patients at high-risk of developing HCC (e.g., those with CHB-related cirrhosis) should enter a surveillance program consisting of ultrasonography with or without the measurement of the serum alpha-

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Received 26 December 2023 Revised 28 March 2024 Accepted 28 March 2024
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https://doi.org/10.33192/smj.v76i4.266951

fetoprotein (AFP) level every 6 months to enable the treatment of potentially treatable disease.[6-8] Despite this recommendation, the surveillance rate remains low at approximately 20% in the US, up to 65% in the UK, and approximately 26% in China.[9-12]

The HCC surveillance rate in Thailand is unknown. In this study, we aim to assess the HCC surveillance rate and compliance in patients with CHB in Thailand, and to identify patient and physician characteristics that could influence the HCC surveillance rate and compliance in such patients.

MATERIALS AND METHODS

Study design and patient population

This retrospective cohort study included consecutive patients with CHB who were monitored for at least one year at Songklanagarind Hospital, a tertiary care university hospital in Thailand between January 2011 and December 2019. The start date of 2011 was chosen to allow time for implementation of the 2010 AASLD guidelines, which include HCC surveillance every 6 months. Patients with CHB were included in the study if they were eligible for HCC surveillance according to the AASLD or EASL recommendations as follow: 1) male aged 40 years or older and female aged 50 years or older, 2) adult patients (aged 18 years or older) with CHB who had a family history of HCC in their first-degree relative(s), and 3) CHB-related cirrhosis.[6,7] If two or more surveillance indications were met, the patients would be categorized for the indication associated with the highest risk of HCC according to the AASLD guideline. CHB patients were identified via the Hospital Information System using the International Classification of Diseases Tenth (ICD-10) Revision codes, and the eligibility of each patient was determined after chart review. Demographic, clinical, and surveillance data were retrieved by the Division of Digital Innovation and Data Analytics (DIDA), Faculty of Medicine, Prince of Songkla University, and double-checked by investigators.

The study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkhla University, Songkhla, Thailand (REC.63-189-14-4). The informed consent was waived by the HREC due to retrospective study of de-identified patients. This research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

All CHB diagnoses by ICD-10 were verified by laboratory results of having positive HBsAg or HBV DNA on two occasions, 6 months apart, or review of the physicians' note of the diagnosis of CHB in medical records. Patients with cirrhosis were defined by either histologically, radiologically, non-invasive measurement of liver stiffness by transient elastography of more than 12.5 kPa, or having cirrhotic complications such as ascites, hepatic encephalopathy, and esophageal varices. HCC was diagnosed and staged according to the 2018 AASLD criteria.[6]

The exclusion criteria were follow-up time at our center for less than 1 year, diagnosis of HCC within 6 months of the first visit, or imaging not performed at Songklanagarind Hospital.

Definitions of surveillance and adherence

Surveillance was defined as liver imaging, including ultrasonography, computed tomography, or magnetic resonance imaging, performed every 6 months according to the AASLD and EASL guidelines with or without measurement of the serum alpha-fetoprotein level.[6,7]

The rate of adherence with surveillance program was assessed using the percentage of time up-to-date with surveillance (PTUDS).[9] To calculate the PTUDS, a patient was credited with 6 months of surveillance following any hepatobiliary imaging. The 6-month clock was restarted if a test was performed before completion of the previous 6-month interval. For example, a patient who was followed-up from January 1, 2019 to December 31, 2019 and had abdominal ultrasound performed on January 1, 2019 and December 30, 2019 would be categorized as being up-to-date with surveillance for 66.7% of his or her follow-up period (12/18 months).

The follow-up duration was defined as the time between the visit at which the study inclusion criteria were deemed to be met and the last day of follow-up until December 2019 or to the date of diagnosis of HCC plus a 6-month credit thereafter.

Study variables

Several variables assumed to have an influence on PTUDS were pre-selected: sex, age (including age at the time of diagnosis and age at the time of starting surveillance), reimbursement status, family history of HCC in first-degree relative(s), indication for HCC surveillance, background medical comorbidities, physician's subspecialty, and travel distance. The physicians' subspecialties were categorized into internal medicine (defined as not having the Thai Board of Gastroenterology certification, but certified Thai board of Internal Medicine), gastroenterology (board-certified internists who were in training for or already had received Thai Board of Gastroenterology certification) Travel distance (defined as the distance between the center of the patient's residential area to Songklanagarind Hospital) was modeled as a continuous

variable and categorized into quintiles based on an estimated duration of travel by car.

Statistical analysis

We calculated the sample size required using the finite population mean formula. With a population size of 5,000 (from total hospital number with diagnosis of CHB) and a standard deviation derived from Goldberg *et al.* of 21.5, along with an error margin of 2, we determined a sample size of 408 while maintaining a significance level of 0.05 and a power of 0.80.

Descriptive statistics were used; categorical variables were reported as number (percentage) and continuous variables were reported as mean+SD or median (interquartile range [IQR]). To compare PTUDS among groups, we used either the Mann-Whitney U-test or Student's t-test as applicable. A univariable linear regression model was used to estimate the beta coefficient and 95% confidence interval (CI) for each variable to predict its relationship with the continuous outcome of PTUDS. All variables with a p-value <0.05 from univariate analyses were then included in the multivariable linear regression model. All statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria, 2021).

RESULTS

Patient characteristics

We screened 542 patients by ascending hospital number. Of these, total 531 patients with CHB who were followed up for more than a year and fulfilled an indication for HCC surveillance were eligible for the study. The sex distribution was slightly male predominant (male 54.5%, female 45.5%) (Table 1). The mean age of the patients at an initiation of surveillance program was 55.5 ± 9.26 years and the median follow-up duration was 7.6 (IQR 4.5 - 9.0) years. The median number of clinical visits for CHB per year was 3.4 (IQR 2.7 - 4.3). The most common reimbursement scheme was civil servants (71.4%). Ten percent of the cohort had a family history of HCC in first-degree relatives. The most common indications for surveillance were male sex and age 40 years or older (41.6%), female sex and age 50 years or older (29.0%), and cirrhosis (22.6%). Family history of HCC was the sole indication for surveillance in only 6.8% of the entire cohort.

Most of the patients in the cohort was free of medical comorbidities at baseline. Hypertension and diabetes mellitus were the leading co-underlying diseases in 20.3% and 13.3%, respectively. The patients were followed up by gastroenterology subspecialists (88.9%) more than by internal medicine specialists (11.1%).

HCC surveillance adherence rates

The median PTUDS in an entire cohort was 70.6% (IQR 54.9 - 81.4%). Cirrhosis was the indication with the highest rate of PTUDS at the median PTUDS of 74.0%, compared with 68.9% for the remaining indications (Fig 2). The median PTUDS for the internal medicine subspecialty was 41.7% (IQR 30.1 – 68.2%) and that for gastroenterology was 71.8% (IQR 58.2 – 81.6%) ($p < 0.001$). Among gastroenterologists, the median PTUDS was 76.5% for hepatologists vs. 69.0% for non-hepatology gastroenterologists ($p < 0.001$). (Fig 3)

The overall compliance rate for the patients to the surveillance program was 97.2%, with 443 patients (83.4%) had 100% compliance rate, 68 patients (12.8%) had compliance rate of 80% or more, and 20 patients (3.8%) had less than 80%.

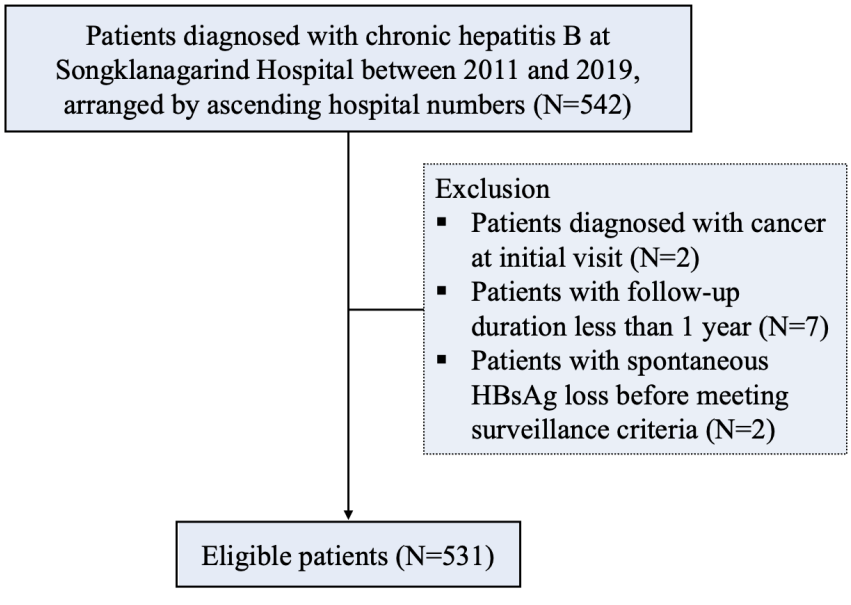

Fig 1. Study flow

TABLE 1. Patient demographic and clinical characteristics.

Variables	Total (n = 531)
Male Sex, n (%)	290 (54.5%)
Age at diagnosis (years)	49.0±12.0
Age at surveillance (years)	55.5±9.26
Visits per year, n (%)	
1-2	330 (62.2%)
>2-4	32 (6.0%)
>4	169 (31.8%)
Travel distance quintile (km), n (%)	
0–40	248 (46.6%)
41–100	83 (15.6%)
101–180	119 (22.6%)
181–300	68 (12.8%)
>301	13 (2.4%)
Reimbursement, n (%)	
Self Payment	55 (10.3%)
Universal Coverage	79 (14.9%)
Civil Servant	379 (71.4%)
Social Security	18 (3.4%)
Family History of HCC[a], n (%)	55 (10.4%)
Indication, n (%)	
Male, age 40 years or older	221 (41.6%)
Female, age 50 years or older	154 (29.0%)
Family history of HCC	36 (6.8%)
Cirrhosis	120 (22.6%)
Underlying disease, n (%)	
Hypertension	108 (20.3%)
Diabetes mellitus	71 (13.3%)
Cardiovascular disease	9 (1.69%)
Chronic kidney disease	8 (1.50%)
Stroke	1 (0.19%)
Cancer[b]	25 (4.70%)
HBV/HCV co-infection	4 (0.75%)
HIV	11 (2.06%)
Specialty, n (%)	
Internal medicine	59 (11.1%)
Gastroenterology or hepatology	472 (88.9%)

Quantitative variables are expressed as the mean and standard deviation and categorical variables as the count and proportion. [a]First-degree relative. [b]All cancers except HCC. HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus

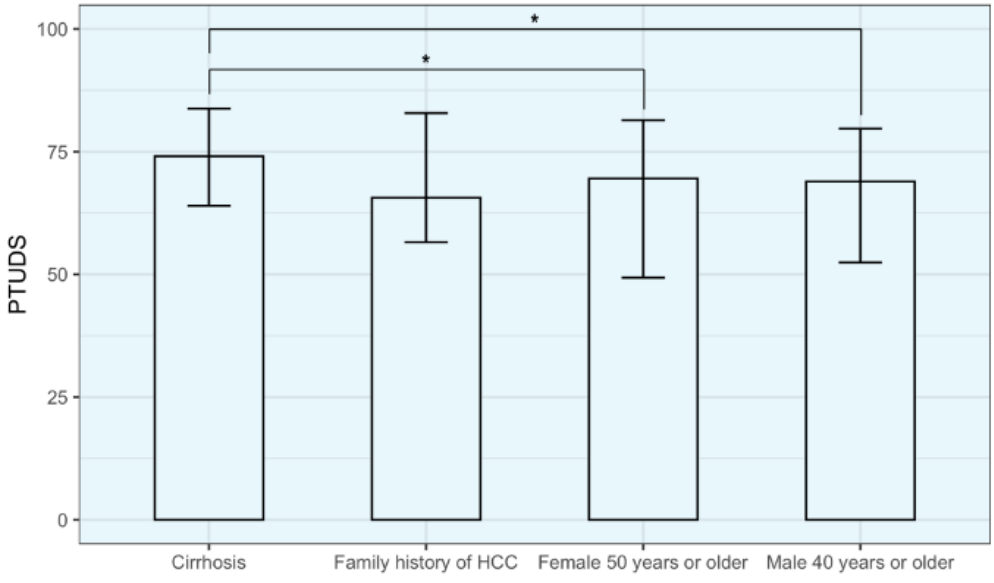

Fig 2. Median PTUDS by Surveillance Indication; *P<0.05; PTUDS: percentage of time up-to-date to HCC surveillance

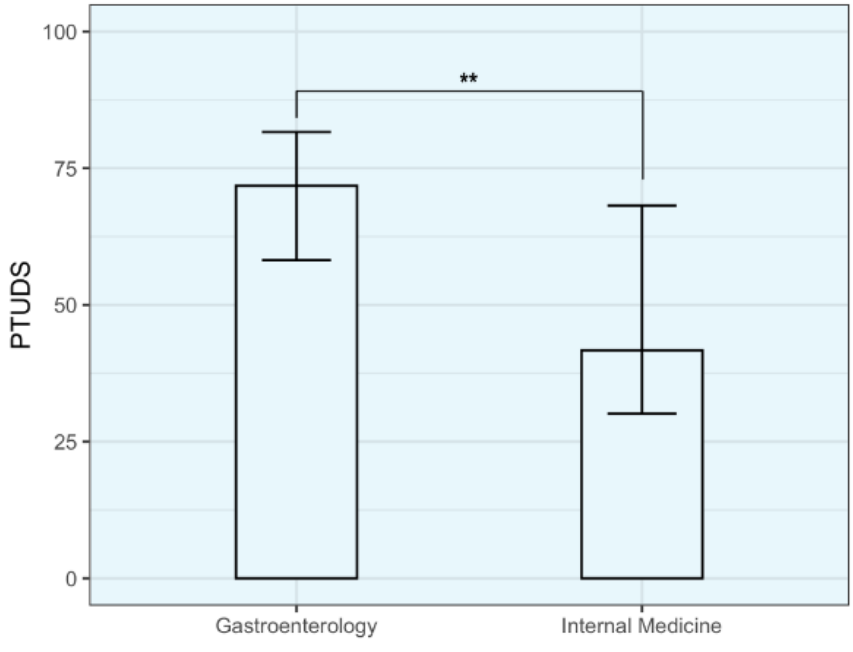

Fig 3. Median PTUDS by Physician's Subspecialty; **P<0.001

Factors associated with HCC surveillance

Univariate analyses of factors associated with an increased HCC surveillance rate revealed that more-than-two clinical visits per year, the civil servant reimbursement scheme, cirrhosis as the surveillance indication, and gastroenterology subspecialty were significant positive predictors (Table 2). Having Human immunodeficiency virus (HIV) co-infection was significantly associated with a lower HCC surveillance rate in the univariate analysis. Age at the time of surveillance initiation and travel distance quintile were not a significant predictor of surveillance rates.

When factors that were significant in univariate analyses were evaluated in the multivariable analysis, more-than-two clinical visits per year, the civil servant reimbursement scheme, cirrhosis as an indication for surveillance, and being followed-up with gastroenterology specialists remained significantly associated with an increased HCC surveillance rate (Table 2). However, HIV comorbidity was no longer statistically significant in the multivariable analysis.

Incidence and characteristics of HCC

HCC was detected during surveillance imaging in

TABLE 2. Factors associated with surveillance of hepatocellular carcinoma.

Variables	Univariable analysis		Multivariable analysis	
	Beta coefficient (95% CI)	P values	Beta coefficient (95% CI)	P values
Male Sex	-0.82 (-4.39 to 2.75)	0.65		
Age at diagnosis	0.12 (-0.03 to 0.26)	0.12		
Age at surveillance				
<40	Reference	0.06		
≥40	8.71 (-0.59 to 18.0)			
Visits per year		<0.001		
1-2	-19.0 (-26.4 to -11.6)	<0.001	-18.4 (-25.3 to -11.6)	<0.001
>2-4	Reference		Reference	
>4	0.55 (-3.24 to 4.33)	0.78	-0.13 (-3.69 to 3.43)	0.94
Travel distance (km)		0.91		
0-40	Reference			
41-100	-0.69 (-5.90 to 4.52)			
101-180	1.10 (-3.48 to 5.67)			
181-300	-1.33 (-6.95 to 4..29)			
>301	-3.21 (-14.9 to 8.47)			
Reimbursement		0.008		
Self-Payment	Reference		Reference	
Civil Servant	10.0 (4.16 to 15.9)	<0.001	8.81 (3.48 to 14.2)	0.001
Social Security	11.0 (0.02 to 15.9)	0.049	9.59 (-0.51 to 19.7)	0.06
Universal Coverage	7.21 (0.08 to 14.3)	0.047	5.65 (-1.02 to 12.3)	0.10
Family History of HCC[a]	-0.14 (-5.82 to 5.54)	0.96		
Indication		<0.001		0.003
Non-cirrhosis	Reference		Reference	
Cirrhosis	7.19 (2.97 to 11.4)		6.06 (2.09 to 10.0)	
Underlying disease				
Hypertension	-1.93 (-6.34 to 2.48)	0.39		
Diabetes mellitus	-1.62 (-6.84 to 3.60)	0.54		
Cardiovascular disease	8.29 (-5.46 to 22.0)	0.24		
Chronic kidney disease	-0.08 (-14.7 to 14.5)	0.99		
Stroke	8.02 (-33.0 to 49.0)	0.70		
Cancer[b]	1.94 (-6.45 to 10.3)	0.65		
HBV/HCV co-infection	-11.2 (-34.9 to 12.5)	0.35		
HIV	-23.5 (-35.9 to -11.2)	<0.001	-11.0 (-22.9 to 0.88)	0.07
Specialty		<0.001		<0.001
Internal medicine	Reference		Reference	
Gastroenterology	20.1 (14.7 to 25.5)		20.4 (14.8 to 25.9)	

[a]First-degree relative. [b]All cancers except HCC. HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; CI, confidence interval

13 patients (2.4%) accounting for incidence rate of 3.7 per 1,000 person-years. Classifying patients by indication for surveillance, 2 were male aged 40 years or older, 1 was female aged 50 years or older, and 10 were cirrhosis. The mean PTUDS for these patients was 75.9 ±13.1%. All of them had been under the care of a gastroenterologist at the time of diagnosis of HCC. Four of these 13 patients (30.4%) developed HCC in a non-cirrhotic liver. The mean time interval between the start of surveillance and diagnosis of HCC was 4.4 years. Almost all of the HCCs detected (12 out of 13) were very early to early stage (Barcelona clinic liver cancer staging 0 to A).

DISCUSSION

This retrospective study is the first to report the rate of adherence with HCC surveillance in patients with CHB in Thailand. For a median follow-up duration of 7.6 years, the median overall adherence with HCC surveillance as defined by PTUDS in our study was 70.6%, which was quite decent compared with previous reports. Goldberg et al. reported the mean PTUDS of any liver imaging in patients with cirrhosis in the US to be 23.3% with a mean follow-up duration of 4.7 years.[9] The strongest predictor of adherence in their study was being followed-up by a specialist in gastroenterology or infectious diseases. The difference between the mean PTUDS in the study by Goldberg et al. and that in our cohort probably reflects a difference in the study population and the clinical setup, as the patients in the study by Goldberg et al. were diagnosed with cirrhosis of various etiologies and followed up at their local hospital, whereas the majority of our patients being diagnosed with non-cirrhotic CHB and followed up at the tertiary-care referral center. One of the factors associated with increased PTUDS was similar, namely, a number of specialty visit, although most specialists in our cohort were gastroenterologists. However, a study by Tran et al. conducted at a university medical center also reported a low rate of adherence with HCC surveillance in patients with chronic hepatitis C cirrhosis, as only 24.4% underwent HCC surveillance every 6 months and 44% received HCC surveillance every 12 months.[10] Interestingly, Asian ethnicity was a predictor of a better surveillance adherence in the study by Tran et al., which might be associated with the increased PTUDS rate in our study, as all of our patients in the cohort were Asian. A recent systematic review of cohort studies evaluated the HCC surveillance rate reported similar results, with an overall surveillance rate of 24.0% and a pooled surveillance rate of 73.7% in studies that included subspecialty care.[13]

The factors associated with a higher adherence rate in our study, such as cirrhosis as an indication for surveillance and follow-up by gastroenterology specialists, underscore the importance of knowledge gap regarding indications for HCC surveillance in high-risk groups, especially the non-cirrhotic population. Thus, implementing an educational program for physicians on HCC surveillance and indications might be beneficial in increasing adherence rates within the community. These findings are also in line with those of other studies.[14-17] The patient-reported barriers associated with receipt of HCC surveillance revealed in other studies were also demonstrated in our study.[18,19]

To further improve the adherence rate of the surveillance program based on our findings, scheduling patients for more than two clinical visits per year could increase the possibility of ultrasound being performed every six months and potentially improve the patient-doctor relationship in the process. The finding that reimbursement scheme of civil servant exhibited higher adherence rates compared to other group was unsurprising due to the ease of medical access to our institution. For instance, patients with universal coverage scheme were required to obtain a referral letter from their local hospital once every year before visiting our center. Interestingly, the distance patients traveled to the hospital did not significantly impact adherence in our study, possibly due to all patients in our cohort being from the lower southern regions of Thailand.

This study had several strengths. First, in contrast with most of the previous studies, which have only reported the surveillance rate in cirrhotic populations, we assessed the HCC surveillance rate in both non-cirrhotic and cirrhotic patients with CHB. Second, the median follow-up duration in our cohort was long and reflected the real-world clinical scenario. Third, this is the first study to report the rate of adherence with HCC surveillance in Thailand, and the findings can be used to improve awareness of the need for surveillance in the country.

The study also had several limitations. Our study was conducted at a single referral center, so its results may not be generalizable to other health care systems. The indications for imaging during the follow-up period were not limited to the surveillance purpose and could include computed tomography performed for an evaluation of the abdominal organs as of other medical or emergency conditions. Therefore, the PTUDS may have been overestimated in some patients. Additionally, the time interval between a clinic appointment and imaging, which has been shown to be associated with the likelihood of adherence with surveillance, was not

investigated. However, almost all imaging ordered in our cohort was eventually performed. Lastly, since this study was a retrospective cohort utilizing the hospital information system from Songklanagarind Hospital, there were no records of education level or economic status available for retrieval, which might influence adherence to HCC surveillance.

In conclusion, we found that the adherence rate to HCC surveillance in our cohort was 70.6%. This study demonstrated the importance of the literacy regarding indications for HCC surveillance, especially in non-cirrhotic patients and those who were not under the care of a gastroenterology specialist. These findings could further guide the implementation of health policy to increase the dissemination of HCC surveillance nationwide and contribute to improved patient survival.

ACKNOWLEDGEMENTS

We acknowledge Prince of Songkla University for the resources in completing this study. The abstract of this study was published in the Annual Health Research International Conference 2022 at the Faculty of Medicine, Prince of Songkla University.

Declarations

Funding

None to declare.

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author's contributions

PF and NC made substantial contributions to the study concept and design, collecting data, analysis and interpretation of data, and drafting of the manuscript. PS, SJ, and AK made substantial contributions to interpretation of data and critical revision of the article. All authors contributed to critical revisions and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkhla University, Songkhla, Thailand (REC.63-189-14-4). The informed consent was waived by the Human Research Ethics Committee (HREC), Faculty of Medicine, Prince of Songkhla University due to retrospective study of de-identified patients. This research was conducted in accordance with both the Declarations of Helsinki and Istanbul.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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