Factors associated with nonadherence to surveillance for hepatocellular carcinoma among patients with hepatic C virus cirrhosis, 2000–2015

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Abstract

Hepatocellular carcinoma (HCC) surveillance can detect the early stage of tumors and lead to improved survival. Adherence to guideline-concordant HCC surveillance is crucial in at-risk populations, including patients with hepatic C virus (HCV) cirrhosis. This study was conducted to identify patient and provider factors associated with nonadherence to HCC surveillance in patients with HCV cirrhosis. Data were primarily obtained from the Taiwan National Health Insurance Research Database for the 2000 to 2015 period. Adult patients newly diagnosed as having HCV cirrhosis between 2003 and 2012 were enrolled. Each patient was followed up for 3 years and until the end of 2015. Annual HCC surveillance was defined as the uptake of an abdominal ultrasound and alpha-fetoprotein (AFP) test annually during the 3-years follow-up. Nonannual surveillance was defined as the lack of an annual abdominal ultrasound and AFP test during the same 3-years period. Multinomial logistic regression models were applied to determine factors influencing adherence or nonadherence to annual HCC surveillance. We included a total of 4641 patients with HCV cirrhosis for analysis. Of these patients, only 14% adhered to annual HCC surveillance. HCC surveillance improved in later years, compared with the earlier phases of the study period. Patients with HCV cirrhosis comorbid with coronary artery disease (CAD) or chronic obstructive pulmonary disease (COPD) or those with a relatively high number of comorbidities had a significantly higher likelihood of nonadherence. Patients who primarily received care from internists were significantly less likely to exhibit nonadherence to annual HCC surveillance compared with patients receiving care from physicians of other specialties. Patients who primarily received care from physicians practicing in larger hospitals were significantly less likely to exhibit nonadherence. HCC surveillance rates remain unacceptably low among high-risk patients, and our findings may be helpful in the development of effective interventions to increase HCC surveillance. The effective incorporation of HCC surveillance into routine visits for other chronic comorbidities, particularly for CAD or COPD, may be crucial for increasing HCC surveillance.

Abbreviation: AFP = alpha-fetoprotein, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, HCC = hepatocellular carcinoma, HCV = hepatitis C virus.

Keywords: CAD, cirrhosis, COPD, HCC, HCV, nonadherence, surveillance

1. Introduction

Chronic hepatitis B (CHB) was the main etiology of Hepatocellular carcinoma (HCC) in Taiwan. However, after Taiwan has launched a series of HCC prevention policies including, a universal hepatitis B vaccination program since 1984, universal health care since 1995, and a national viral hepatitis therapy program since 2004, the estimated relative contributions of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection to HCC incidence after the year 2009 were 51.4%

versus 48.6%, respectively, which were very close.[1] The crude incidence rate of HCC in Taiwan was 47.05 per 1,00,000 person-years and the crude mortality rate was 35.48 per 1,00,000 person-years in 2016.[2] Therefore, it is critical to obtain more insights about HCV-related HCC surveillance practice in Taiwan.

HCC surveillance can detect early-stage tumors, determine suitability for curative therapy, and lead to improved survival[3–5] Expert guidelines have recommended screening services for HCC surveillance, including semiannual abdominal ultrasound

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examination and alpha-fetoprotein (AFP) tests, among emerging at-risk individuals such as patients with HCV cirrhosis.[4–8] Patients with HCV cirrhosis remain at risk of HCC[9,10]; therefore, adherence to guideline-concordant HCC surveillance is crucial in such patients. However, less than 30% of patients with cirrhosis receive semiannual screening for HCC surveillance.[11,12] The low adherence to HCC surveillance poses a threat to HCC prevention and prognosis.

Adherence to HCC guidelines and surveillance is suboptimal and lower than expected in clinical practice.[13,14] Timely evaluation for cirrhosis in at-risk populations could improve outcomes for patients with HCC.[15] Studies have mostly focused on analyzing HCC surveillance among at-risk populations but have not specified the corresponding etiologies. Because of the heterogeneity in disease progression among different etiologies, conducting more analyses on patients with a specific etiology is crucial. Although HCV contributes substantially to the increasing global prevalence of HCC, only a few studies have elucidated factors influencing HCC surveillance among patients with HCV cirrhosis.[12,16,17]

Multiple individual- and provider-level factors affect HCC surveillance among patients with cirrhosis, including gender,[18] race,[19] patient involvement in the decision process,[18] outpatient clinical visits,[20] living areas,[14,20] income,[20] liver disease etiology,[19,20] liver disease severity,[12] insurance status,[14,19] physician specialty,[11,14,20] physician practice pattern and location,[20] and suboptimal knowledge of effective HCC therapy options.[21] However, the increasing prevalence of chronic conditions may also be a hidden factor contributing to nonadherence and suboptimal adherence to HCC surveillance among patients with HCV cirrhosis. Only 1 US-based study using data from the U.S. Department of Veterans Affairs investigated the influence of comorbidities on HCC surveillance among patients with HCV-related cirrhosis.[12] However, the findings of the limited studies conducted in the West might not be generalizable to Asian countries because of differences in health-care systems and cultures between these regions; hence, the scope of such research should be expanded to Asian countries to provide findings that can help reduce the global HCC incidence. Moreover, physician practice setting may be a factor influencing an individual's health-care-seeking behavior and must thus be explored. Despite the recognition of the aforementioned risk factors, the rate of HCC surveillance is still suboptimal.

Most population-based studies have considered regular surveillance as involving either an abdominal ultrasound or an AFP test.[12,14,16,17,20,22,23] However, according to the recommendation provided by the 2017 Asian Pacific Association for the Study of Liver,[24] an AFP test in combination with an abdominal ultrasound would provide an additional benefit of detecting early HCC.[25] Therefore, abdominal ultrasound examination along with an AFP test must be considered in the exploration of factors influencing nonadherence to HCC surveillance in patients with HCV cirrhosis.

To fill the aforementioned research gaps, we conducted a nationwide retrospective cohort study focusing on the at-risk group of patients with HCV cirrhosis. Specifically, we conducted this study to identify the annual surveillance rate and assess factors influencing nonadherence in patients with HCV cirrhosis at both the individual level and provider level under the Taiwan National Health Insurance (NHI) program, a typical single-payer universal health coverage system. To determine the influence of physician practice setting on health-care-seeking behavior, we also explored the characteristics of physician practice settings, including health-care providers' accreditation level and ownership and area-level physician density. Moreover, to precisely identify more unexplored factors influencing nonadherence to HCC surveillance in patients with HCV cirrhosis, we considered HCC surveillance as regular surveillance involving abdominal ultrasound examination along with an AFP test. Our study can expand the scope of previous research to an Asian context.
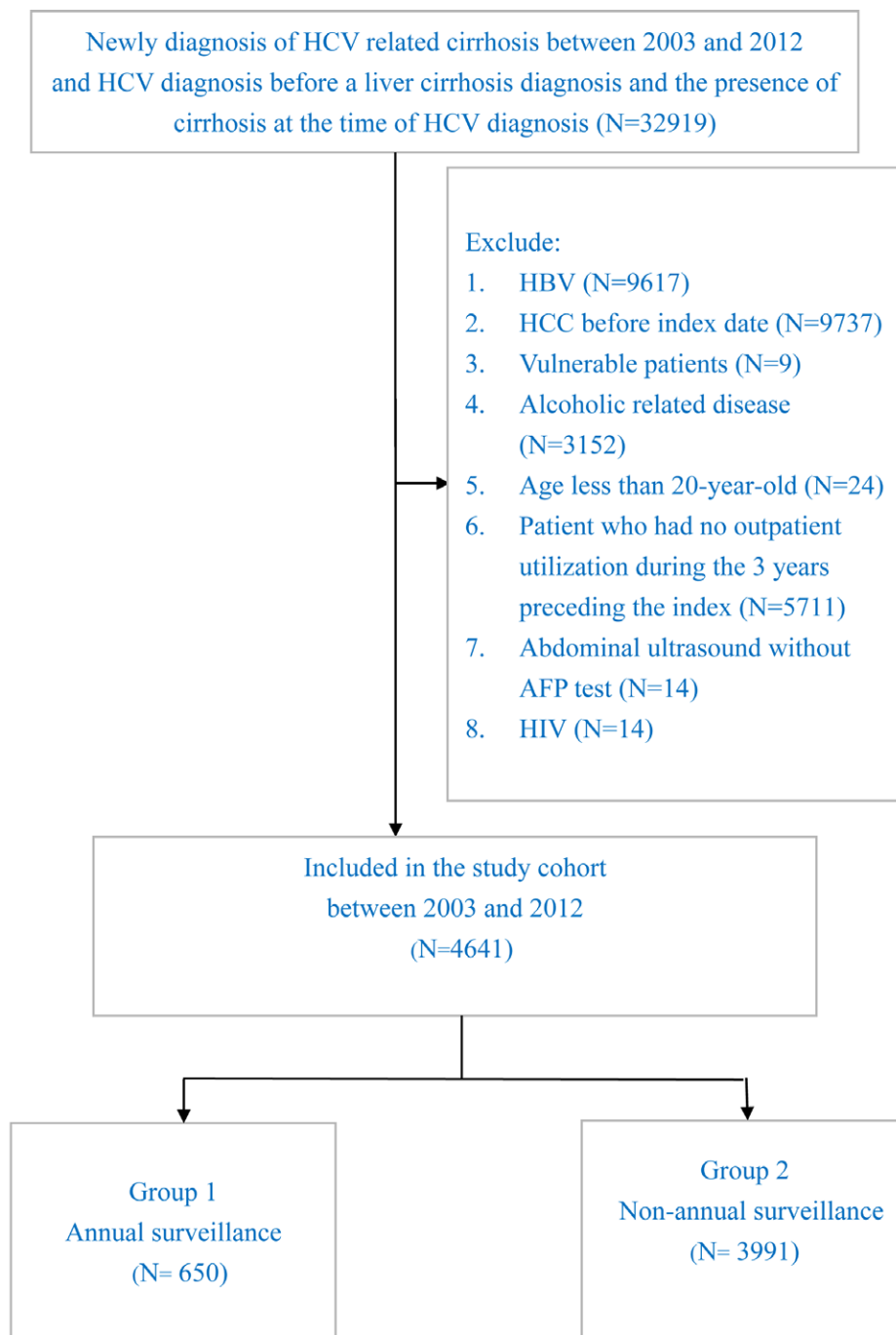
2. Methods

2.1. Data source

The primary data source was the 2000 to 2015 National Health Insurance Research Database (NHIRD), which is managed by the National Health Research Institutes and available for research purposes with a proper application and review process. Taiwan's NHI program provides universal health insurance to all residents in Taiwan (approximately 23 million people). The NHIRD contains the enrollment and claims data of all NHI program enrollees. The claims data provide information on the date of visit or hospitalization; diagnosis information based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes; types of health providers; and types and costs of all health-care services, medical procedures, drug prescriptions, and itemized expenditures. We used specific files in the NHIRD, such as enrollment files and physician and facility registries, in this study. The enrollment files provide information on each person's monthly wage and category, location, and date of and reason for unenrollment. The NHI medical personnel registry records each physician's date of birth, gender, and specialty. The NHI hospital registry provides information on the accreditation level of each physician's practice setting. Physician and patient identification numbers are all encrypted in the database.

2.2. Study population

This nationwide retrospective cohort study included the data of adult patients who were newly diagnosed as having HCV-related cirrhosis (*ICD-9-CM* codes 571.5, 571.6) between January 2003 and December 2012. We included the data of patients with an HCV diagnosis (*ICD-9-CM* codes V02.62, 070.41, 070.44, 070.51, and 070.54) before a liver cirrhosis diagnosis and the presence of cirrhosis at the time of HCV diagnosis. Each patient was followed up for 3 years and until the end of 2015. The index date was considered the date of the first abdominal ultrasound examination and AFP test in the cohort of patients newly diagnosed as having HCV cirrhosis. We excluded patients aged younger than 20 years and patients who had a history of chronic hepatitis B (*ICD-9-CM* codes 070.2, 070.3, V026.1, V026.9, V026.1, 070.22, 070.32, V026.9), alcohol-related diseases (*ICD-9-CM* codes 291, 303, 305.0, 571.0, 571.1, 571.2, 571.3, 303.0, 303.9), and human immunodeficiency virus (HIV) (*ICD-9-CM* codes 042) between January 1, 2000, and December 31, 2015. We also excluded patients who had no outpatient utilization during the 3 years preceding the index date and patients who had a history of HCC prior to the index date. Finally, we excluded vulnerable patients, including patients who were in a bedridden state, had long-term indwelling nasogastric tubes and urinary catheters, had a tracheostomy, or had a history of ventilator use between January 1, 2000, and December 31, 2015. The final sample included 3478 patients (Fig. 1).

2.3. Variables

Adherence to HCC surveillance was defined as a patient's annual uptake of abdominal sonography and AFP within the 3-years follow-up. Individual adherence was categorized into 2 levels: undergoing annual surveillance (adherence) and not undergoing annual surveillance (nonadherence). Annual surveillance was defined as the annual uptake of an abdominal ultrasound and AFP test for HCC surveillance during the follow-up period. Nonannual surveillance was defined as the lack of an annual uptake of an abdominal ultrasound and AFP test for HCC surveillance during the 3 years following the index date.

Newly diagnosis of HCV related cirrhosis between 2003 and 2012
and HCV diagnosis before a liver cirrhosis diagnosis and the presence of
cirrhosis at the time of HCV diagnosis (N=32919)

Exclude:
1. HBV (N=9617)
2. HCC before index date (N=9737)
3. Vulnerable patients (N=9)
4. Alcoholic related disease (N=3152)
5. Age less than 20-year-old (N=24)
6. Patient who had no outpatient utilization during the 3 years preceding the index (N=5711)
7. Abdominal ultrasound without AFP test (N=14)
8. HIV (N=14)

Included in the study cohort
between 2003 and 2012
(N=4641)

Group 1
Annual surveillance
(N= 650)

Group 2
Non-annual surveillance
(N= 3991)

HCV: hepatic C virus; HBV: hepatitis B virus; HCC: hepatocellular carcinoma,
HIV: human immunodeficiency virus

Figure 1. Flowchart of patient selection.

2.4. Patient characteristics

Patient age, sex, preexisting comorbidities, health-care-seeking behavior, and socioeconomic status (SES) were analyzed. The comorbidities identified in this study were diabetes mellitus (DM), dyslipidemia, psychiatric disorders, coronary artery disease (CAD), and chronic obstructive pulmonary disease (COPD) within the 3 years preceding the index date. Patients with preexisting DM, dyslipidemia, or psychiatric disorders were defined as those with 1 inpatient diagnosis of one of the aforementioned diseases or with at least 2 outpatient visits for one of

the aforementioned diseases or disease-related prescriptions. Patients with CAD and COPD diseases were defined as those with 1 inpatient diagnosis of one of the aforementioned diseases or with at least 2 outpatient visits for one of the aforementioned diseases. We included 2 variables for health-care-seeking behavior: outpatient utilization and routine medical checkups. Outpatient utilization was based on the number of outpatient visits made by a patient within the 3 years preceding the index date; it was categorized into 3 levels: low, medium, and high. Routine medical checkups were defined as the uptake of any

routine medical checkup within the 3 years preceding the index date. Furthermore, we used the NHI monthly wage/category as a proxy of SES. Patients with a well-defined monthly payroll were categorized into 3 groups according to their monthly payroll level: >NT$40,000, NT$40,000 to NT$20,000, and < NT$20,000 (NT$: New Taiwan dollars; US$1 = approximately NT$30.24). Patients without a well-defined monthly payroll were categorized into 2 groups according to their insurance categories: union or association members and other.[26] The availability of resources near a patient's residential area may also influence the likelihood of their adherence. Therefore, we included 1 area characteristic, namely physician density, in our analyses. We used township-level physician density derived in 2013, which was defined by the number of licensed Western medicine physicians per square kilometer and categorized into quintiles.

2.5. Provider characteristics

We considered a patient's principal health-care provider as the provider whom the patient visited the most during the 3 years preceding the index date. In addition to including physician age, sex, and specialty, we included the characteristics of health-care providers' practice settings in our analyses. Under the NHI program in Taiwan, medical institutions are classified according to their quality, staffing, and infrastructure. Accordingly, accreditation level was divided into 2 categories: medical center and regional hospitals and; district hospitals and clinics. No referral is necessary for accessing higher-level providers or specialists in Taiwan. Residents in Taiwan enjoy complete freedom in choosing their providers under the NHI program.[27,28] Hospital ownership was considered either public or private.

2.6. Statistical analysis

Herein, the distribution of baseline characteristics is expressed as frequencies and percentages. Multinomial logistic regression models were applied to determine factors associated with a patient's adherence (adherence or nonadherence to annual HCC surveillance). Furthermore, we conducted a sensitivity analysis by treating the dependent variable as a categorical variable (annual surveillance, irregular surveillance, and no surveillance during the 3-years follow-up period). Odds ratios (ORs) and 95% confidence intervals (CIs) along with their P values were calculated. A 2-sided P value of < 0.05 was considered statistically significant. All statistical analyses were conducted using SAS statistical software (Version 9.4; SAS Institute, Cary, NC).

2.7. Ethical approval

The study protocol was approved by the Taipei City Hospital Research Ethics Committee (TCHIRB-10707114-W).

3. Results

This study included a total 4641 patients with HCV cirrhosis for analysis. Only a minority of the patients (14.01%) adhered to annual surveillance (Table 1). The proportion of non-adherence to surveillance for cirrhotic HCV-related HCC decreased over time, from 94.22% between 2003 and 2005 to 83.19% between 2009 and 2012 (Fig. 2). Our multinomial logistic regression models revealed that after adjustment for other variables, patients aged at 75 years or older (OR, 1.63; 95% CI, 1.21–2.19), patients comorbid with CAD (OR, 1.57; 95% CI, 1.12–2.22) and COPD (OR, 1.82; 95% CI, 1.14–2.91) were significantly more likely to not adhere to annual HCC surveillance (Table 2A). Moreover, patients who had undergone a routine medical checkup less likely to exhibit nonadherence (OR, 0.61; 95% CI, 0.51–0.73). Outpatient-care-seeking behavior was

significantly associated with nonadherence to annual HCC surveillance. A higher rate of outpatient care utilization was significantly associated with a higher likelihood of undergoing annual HCC surveillance. Patients with medium (OR, 0.39; 95% CI, 0.30–0.49) or high (OR, 0.35; 95% CI, 0.27–0.45) rates of outpatient care utilization were less likely to exhibit nonadherence. Patients who primarily received care from physicians practicing in larger hospitals (i.e., regional hospitals and medical centers) were significantly less likely to demonstrate nonadherence (OR, 0.78; 95% CI, 0.64–0.96) than did those who primarily received care from physicians practicing in clinics and district hospitals. By contrast, patients who primarily received care from family physicians (OR, 1.91; 95% CI, 1.50–2.43) and physicians of other specialties (OR, 2.44; 95% CI, 1.96–3.05) were significantly more likely to exhibit nonadherence to annual HCC surveillance than did those who primarily received care from internists. Furthermore, we conducted a sensitivity analysis by replacing specific comorbidities with the number of comorbidities in the model; we observed that after adjustment for other factors, a higher number of comorbidities was significantly associated with a higher likelihood of nonadherence. Patients with 1 comorbidity and those with 2 or more comorbidities were 1.51 times (95% CI, 1.20–1.90) and 1.74 times (95% CI, 1.12–2.69) more likely to not adhere to annual HCC surveillance (Table 2B) than did other patients. The results remained unchanged when we further categorized adherence to HCC surveillance during the 3-years follow-up period into 3 categories: annual surveillance, irregular surveillance, and no surveillance.

4. Discussion

By using a nationally representative sample, we investigated factors associated with the uptake of annual HCC surveillance among patients with HCV cirrhosis. Patients with HCV cirrhosis may have a high risk of HCC and must thus undergo ongoing surveillance.[9,10] However, we noted that the majority of the patients with HCV cirrhosis (85.99%) did not receive annual HCC surveillance, which is consistent with the findings of previous studies conducted in other countries.[16,19,20,29] Adherence to HCC surveillance is considerably below the rate recommended by existing guidelines; such guidelines suggest that at-risk patients, including those with cirrhosis, should undergo HCC surveillance every 6 months.[7,8]

Our study on factors influencing HCC surveillance among patients with HCV cirrhosis demonstrated several major findings. First, elderly patient and the presence of severe comorbid conditions in patients with cirrhosis may reduce the likelihood of receiving potentially curative therapy and diminish a physician's surveillance capabilities.[20] Compared to their counterparts, these patients with complex health care needs were more likely to exhibit nonadherence or suboptimal adherence to HCC surveillance possibly due to their limited morbidity, time constraints and the treatment burdens associated with multiple chronic diseases.[12,30] By contrast, patients with DM, dyslipidemia, and psychiatric disorders commonly adhered to HCC surveillance. One possible explanation for this finding is that these 3 conditions are risk factors for nonalcoholic fatty liver disease or nonalcoholic steatohepatitis,[31–36] which increases the risk of HCC. Therefore, abdominal ultrasound and AFP tests are commonly and actively performed in patients with these conditions, especially patients with cirrhosis, during routine visits to healthcare providers. Accordingly, determining strategies for integrating effective HCC surveillance approaches into routine visits for other chronic comorbidities, particularly CAD or COPD, may be critical for increasing HCC surveillance.

Second, we determined that patients who underwent routine medical checkups or had higher rates of outpatient care utilization were significantly more likely to adhere to annual HCC surveillance. Because HCC is likely to progress with no obvious

Table 1

Baseline Characteristics of 4641 HCV cirrhotic patients who received annual surveillance and nonannual surveillance.

	Annual surveillance		Nonannual surveillance	
	n = 650	%	n = 3991	%
Gender:				
Male	248	38.15	1748	43.80
Female	402	61.85	2243	56.20
Age				
<55	123	18.92	762	19.09
55–64	195	30.00	1003	25.13
65–74	199	30.62	1145	28.69
≥75	133	20.46	1081	27.09
Co-morbid condition				
DM	43	6.62	355	8.53
Dyslipidemia	27	4.15	175	4.51
Psychiatric disorder	28	4.31	233	6.19
CAD	43	6.62	392	10.24
COPD	21	3.23	231	5.59
Co-morbid amount				
0	515	79.23	2892	72.46
1	110	16.92	869	21.77
≥2	25	3.85	230	5.76
Medical checkup				
Yes	371	57.08	1701	59.59
No	279	42.92	2290	40.41
Seeking behavior				
Lower	124	23.50	1442	36.91
Middle	268	39.87	1277	31.42
Higher	258	36.63	1272	31.67
Income				
Local enrollees	130	20.00	933	22.13
Union/association member	224	34.51	1462	36.77
<20,000 NT$	42	6.47	250	5.94
20,000–39,999 NT$	163	25.12	879	22.96
≥40,000 NT$	90	13.87	462	12.09
Provider age				
<45	57	8.77	351	8.79
45–54	298	45.85	1467	36.76
≥55	295	45.38	2173	54.45
Provider gender				
Male	614	94.64	3741	93.39
Female	35	5.36	240	6.29
Specialist				
Internist	414	65.07	1782	47.40
Family physician	104	16.14	863	21.36
Other specialty	121	18.78	1246	28.94
Hospital level:				
Clinics and district	205	32.09	1414	37.15
Regional/center	445	67.91	2577	62.85
Ownership				
Public	140	21.54	970	22.82
Private	510	78.46	3021	77.18
Area level				
I	168	25.85	952	23.87
II	127	19.54	915	22.94
III	125	19.23	826	20.71
IV	152	23.38	755	18.93
V	78	12.00	540	13.54
HCV diagnosis yr				
2003	5	0.77	156	3.91
2004	11	1.69	264	6.61
2005	28	4.31	297	7.44
2006	45	6.92	304	7.62
2007	61	9.38	427	10.70
2008	72	11.08	425	10.65
2009	74	11.38	490	12.28
2010	102	15.69	508	12.73
2011	121	18.62	551	13.81
2012	131	20.15	569	14.26

DM = Diabetes mellitus, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, HCV = hepatitis C virus.

Local enrollees = Local government enrollees, Union/association member = Farmers and fishers, Hospital level = Accreditation level of practice setting, Clinics and district = clinics and district hospitals,

Regional and center = regional hospitals and academic medical center, SES = Socioeconomic status, NTD = New Taiwan Dollars, Area level = area level of physician density.
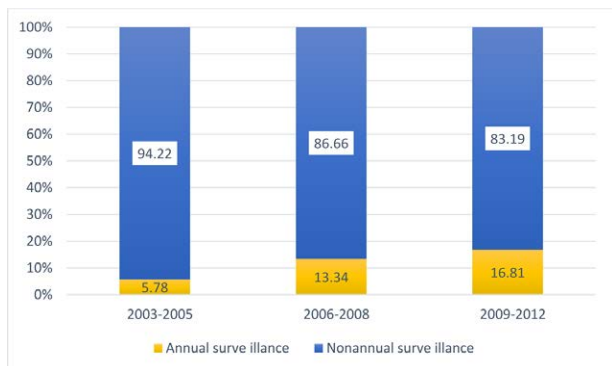
Figure 2. The trend analysis of nonadherence to surveillance for hepatocellular carcinoma among patients with cirrhotic hepatic C virus infection, 2000–2015.

initial symptoms, patients who are more attentive to their health or have more interactions with health-care providers may be more likely to receive regular surveillance.

Third, we observed that provider characteristics play a crucial role in patients' uptake of annual HCC surveillance. Nonadherence to HCC surveillance can be attributed to a provider's failure to identify the silent transition to cirrhosis and to order an abdominal ultrasound and AFP test for HCC.[37] Our results reveal that patients who primarily received care from internists were more likely to undergo annual HCC surveillance compared with who primarily received care from family physicians or physicians of other specialties. Possible reasons for the significant differences in HCC surveillance among physicians of different specialties are training background, knowledge of guidelines, experience caring for patients with cirrhosis, and practice habits.[14,20,38–41] Furthermore, patients who received care in larger hospitals (i.e., medical centers and regional hospitals) demonstrated higher HCC surveillance, a finding that is consistent with

Table 2

Results of multinominal logistic regressions for predicted factors associated with non-annual surveillance versus annual-surveillance in HCV cirrhotic patients.

	Non-annual surveillance			
	Table 2A		Table 2B	
	OR*	95% CI*	OR**	95% CI**
Gender (Ref: female):	1.11	0.93–1.33	1.11	0.93–1.33
Age (Ref:<55)				
55–64	1.02	0.78–1.33	1.02	0.79–1.33
65–74	1.21	0.92–1.60	1.22	0.93–1.61
≥75	1.63	1.21–2.19	1.66	1.23–2.22
Comorbid condition:				
DM	1.28	0.91–1.80		
Dyslipidemia	1.21	0.78–1.86		
Psychiatric disorder	1.21	0.79–1.86		
CAD	1.57	1.12–2.22		
COPD	1.82	1.14–2.91		
Comorbid amount (Ref: 0)				
1			1.51	1.20–1.90
≥2			1.74	1.12–2.69
Medical checkup (Ref: No)	0.61	0.51–0.73	0.61	0.51–0.73
Seeking behavior (Ref: Lower)				
Middle	0.39	0.30–0.49	0.39	0.30–0.49
Higher	0.35	0.27–0.45	0.35	0.27–0.45
SES (Ref: Local enrollees)				
Union/association member	0.97	0.76–1.25	0.97	0.75–1.24
<20,000 NT$	0.87	0.58–1.28	0.87	0.59–1.29
20,000–39,999 NT$	0.83	0.64–1.09	0.83	0.63–1.07
≥40,000 NT$	0.77	0.56–1.04	0.76	0.56–1.03
Provider age (Ref: <45)				
45–54	0.90	0.65–1.24	0.91	0.66–1.25
≥55	1.33	0.97–1.83	1.33	0.97–1.83
Provider gender (Ref: female)	0.99	0.68–1.45	0.99	0.68–1.45
Specialist (Ref: internalist)				
Family physician	1.91	1.50–2.43	1.91	1.50–2.44
Other specialty	2.44	1.96–3.05	2.44	1.95–3.04
Hospital level (Ref: clinics and district)				
Regional/center	0.78	0.64–0.96	0.79	0.64–0.97
Ownership (Ref: private)	0.86	0.69–1.06	0.85	0.69–1.06
Area level (Ref: I)				
II	1.23	0.95–1.59	1.23	0.95–1.59
III	1.18	0.91–1.54	1.19	0.91–1.54
IV	0.87	0.67–1.13	0.87	0.67–1.13
V	1.11	0.80–1.55	1.11	0.80–1.55

DM = Diabetes mellitus, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, HCV = hepatitis C virus.

* Predicted factors associated with non-annual surveillance versus annual-surveillance in HCV cirrhotic patients with comorbid condition.

** Predicted factors associated with non-annual surveillance versus annual-surveillance in HCV cirrhotic patients with comorbid amount.

that of a previous study, which reported that physicians with an academic affiliation had higher rates of HCC surveillance.[20]

Notably, we did not observe considerable differences in adherence to HCC surveillance with respect to SES or residential area, which is inconsistent with the findings of studies conducted in other countries. Because the NHI program provides affordable and flexible access to health services in Taiwan, patients do not experience financial or geographical barriers to HCC surveillance. Consistently low HCC surveillance across various SES strata or geographical areas may be attributed to other factors, which may require further research.[42]

Our study has several strengths. First, we considered HCC surveillance as involving the combined use of an abdominal ultrasound and an AFP test annually for 3 years; the concomitant use of an abdominal ultrasound and an AFP test can facilitate early HCC detection,[4,25,43–45] rendering it the best indicator of adherence to HCC surveillance. By contrast, previous studies have mostly considered HCC surveillance as involving the use of either an abdominal ultrasound or an AFP test and have used 2-years follow-up periods.[12] Second, we enlisted all adult patients newly diagnosed as having HCV cirrhosis. By contrast, previous studies have mostly been limited to specific subpopulations, such as people aged 65 years or older or veterans.[20] Third, we extended the existing knowledge of regular HCC surveillance uptake to an Asian society with universal health coverage. Previous studies have mostly been limited to the United States.

This study has several limitations. First, the lack of severe liver disease in our data may be a possible limitation. Because the benefits of regular HCC surveillance for patients with advanced cirrhosis may be debatable, we limited our sample to patients with newly diagnosed cirrhosis. Second, although existing guidelines recommend the execution of HCC surveillance every 6 months, they also recommend that executing HCC surveillance every 12 months will suffice for patients with HCV cirrhosis returning for regular screening and testing.[46] In addition, a previous study reported that only 13% of patients with cirrhosis received annual surveillance and that less than 2% of patients received semiannual surveillance.[19] In our sample, only 18% of the patients with HCV cirrhosis received an annual abdominal ultrasound and AFP test, which is consistent with the previous study's findings. Therefore, to obtain meaningful analyses of factors associated with regular surveillance, we decided to use annual HCC surveillance instead of semiannual surveillance as the main outcome variable. Third, patient knowledge, attitudes, and perceived barriers may be crucial for HCC surveillance.[47] Although outpatient utilization and health checkups were used as proxies, these 2 proxy indicators may not fully reflect the influences of patient knowledge, attitudes, and perceived barriers. Fourth, owing to data limitations, we were unable to obtain information on physician knowledge, familiarity, or attitudes toward HCC surveillance. We used physician specialty as a proxy for physician training and knowledge. Future research with more comprehensive physician data may help contribute in this regard. Fifthly, using ICD codes alone to identify cirrhosis patients might have excluded patients with undiagnosed cirrhosis. This limitation may lead to an overestimate of true surveillance rate among all patients with cirrhosis as those patients without an ICD code of cirrhosis are less likely to receive HCC surveillance. Sixthly, due to the data limitation, our finding can only serve as a baseline assessment of HCC surveillance practices in pre-direct acting antiviral (DAA) era. Further research with more recent data will help to study how DAA may influence HCC surveillance by comparing surveillance before and after DAA treatment became available, and whether HCC surveillance practice continues after cure if indicated by fibrosis status. Finally, because patients may undergo an abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scan instead of an abdominal ultrasound scan, the rate of regular surveillance for HCC detection may have

been underestimated. However, the National Health Insurance Administration records strict audits of CT and MRI scans due to their high prices. Hence, physicians in Taiwan are unlikely to prescribe CT or MRI scans for regular HCC surveillance. In general, an abdominal CT or MRI scan is warranted if an abnormality exists. Therefore, the bias due to the possibility of underestimation might be low.

To our knowledge, this is the largest population-based study on HCC surveillance among patients with HCV cirrhosis. Comprehensive universal health coverage, presence of comorbidities, health-seeking behavior, and physician training background and practice setting exhibited significant effects on the uptake of annual HCC surveillance among patients with HCV cirrhosis.

In conclusion, our study revealed that the rates HCC surveillance remained unacceptably low and underprescribed in clinical practice. Our findings may help devise an effective intervention to increase the uptake of HCC surveillance.

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