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Master Thesis

以電腦模擬建構對照組評估族群肝癌篩檢效益

Effectiveness of Abdominal Ultrasound Screening Policy for Hepatocellular Carcinoma Evaluated by Computer Simulation with Pseudo Control Design

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Abstract

Background Mass screening for hepatocellular carcinoma (HCC) with abdominal ultrasound (AUS) has been demonstrated in short-term follow-up without using a randomized controlled design. How to have a suitable control group plays an important role in the evaluation of long-term effectiveness of the overall and marginal effectiveness and cost-effectiveness of AUS as well as the recently emerging anti-viral therapy. Such an evaluation has been addressed before by the development of predictive model and also the creation of a computer simulation design characterized by the pseudo-control group in the absence of intervention on AUS and anti-viral therapy.

Aims The objective of this thesis is to

(1) develop a predictive model based on viral and non-viral factors for the risk of HCC;

(2) develop a natural history model for the disease progression of HCC embedded with the risk prediction model developed in (1) and the prognosis model in relation to the survival of HCC in order to form a pseudo-control group in the absence of AUS screening;

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(3) estimate long-term effectiveness and cost-effectiveness of AUS in reducing HCC mortality based on the pseudo-control group;

(4) estimate long-term effectiveness and cost-effectiveness of AUS and anti-viral therapy in reducing HCC mortality based on the pseudo-control group;

(5) estimate long-term effectiveness and cost-effectiveness of AUS and anti-viral therapy in reducing HCC mortality by risk groups based on the pseudo-control group;

Data and methods Data used here are based on a risk score-guided invitation for abdominal ultrasound which has been launched since October, 2008 in Changhua. Subjects aged 45-74 years attended the Changhua community-based integrated screening (CHCIS) program were targeted. Those with high score based on hepatitis virus infection, ALT, AST, type 2 diabetes, platelet count were invited to receive ultrasonography screening performed by board-certified gastroenterologists in town-based health center to identify liver cirrhosis, and suspected HCC cases.

We developed a pseudo-control group by building up the disease natural history of progression of HCC embedded with the risk prediction model for HCC and the survival of HCC by detection modes. The pseudo-control model was further used to

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the development of health economic decision model for cost-effectiveness of various preventive strategies.

Results The main results of this thesis include

(1) The predictive validity of the risk prediction model for HCC is very good on the basis of ROC curve performance with AUC higher up to 0.89 (95% CI: 0.85-0.93);

(2) The observed 8-year HCC mortality reduction with AUS by risk groups together with around 30% coverage rate of anti-viral therapy was around 60% (RR=0.39, 95% CI: 0.32-0.46);

(3) The simulated results by using the pseudo-control group indicate additional contribution of 30% compliance rate of anti-viral therapy (empirical estimate) to HCC mortality reduction was around 22%. The corresponding figures are be raised to 30% and 35% when the compliance rate of anti-viral therapy is enhanced to 50% and 70%, respectively.

(4) The simulated results by using the pseudo-control group show 3% HCC mortality reduction attributable to additional contribution of screening intermediate risk group with AUS when the coverage rate of this group is enhanced from 25% to 75%.;

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(5) The results of health economic decision model show the ICER (incremental cost-effectiveness ratio) values were $22,849 for the administration of AUS, $101,849 for the administration of AUS plus 30% compliance to anti-viral therapy. The corresponding figure for 50% and 70% compliance rate to anti-viral therapy were $141,805 and $181,919, respectively.

Conclusions The population-based screening programme for HCC in Changhua confirmed the validity and feasibility for the developed risk score applied in our screening programme. We further used a computer study design with a pseudo-control group that was developed on the basis of disease natural history of HCC embedded with the predictive model and the survival part of HCC to estimate long-term effectiveness of the overall and marginal effectiveness and cost-effectiveness of AUS and anti-viral therapy.

Keywords: Abdominal ultrasound screening; Anti-viral therapy; Computer Simulation; Effectiveness; Hepatocellular carcinoma

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中文摘要

研究背景　運用腹部超音波進行族群肝癌篩檢對於降低肝癌死亡風險之短期效益在過往的研究中已藉由非隨機分派研究之實驗設計得到證據。然而如何運用合宜對照組對於此腹部超音波族群篩檢策略以及近年來發展之抗病毒治療在長期追蹤之整體與邊際效益與成本效益評估扮演重要的角色。此一評估方法在過往的研究中曾以預測模式之建構結合電腦模擬之研究設計以到建立在未進行腹部超音波與抗病毒藥物之情境下之模擬對照組達到評估之目的。

目的　本研究論文之目的在於

(1) 運用肝病毒以及非病毒之因子發展肝癌預測模型；

(2) 在(1)之風險預測模型下發展肝癌疾病自然進展模型以及肝癌存活之預後模型作為建構未進行腹部超音波篩檢之狀態下的模擬對照組之基礎；

(3) 運用上述之模擬對照組評估腹部超音波篩檢策略對於降低肝癌死亡之長期效益；

(4) 運用模擬對照組評估腹部超音波篩檢結合抗病毒治療對於降低肝癌死亡之長期追蹤效益；

(5) 以模擬對照組評估腹部超音波篩檢結合抗病毒治療對於不同風險族群在降低肝癌死亡之長期追蹤效益。

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材料與方法　本研究所運用之資料乃源於以風險分數為導向之腹部超音波篩檢介入。此一介入計畫於 2008 年 10 月開始於彰化縣執行。該介入策略之目標族群為 45-74 歲，參與彰化社區整合式萬人健檢(Changhua community-based integrated screening, CHCIS)計畫之民眾。各鄉診中之目標族群民眾在運用肝病毒感染、麩丙酮酸轉胺酶(ALT)、麩草醋酸轉胺酶(AST)、第二型糖尿病、血小板計數構成之風險分數區辨之高風險民眾，將邀請接受由腸胃科專科醫師執行之腹部超音波篩檢，以達到偵測民眾中具有肝硬化以及疑似肝癌病患之目的。

本論文發展電腦模擬架構結合肝癌疾病自然史及實證資料發展出的預測模式及存活資料以建構對照組，進一步進行不同肝癌防治策略之成本效益分析。

結果　本論文主要發現歸納以下五點：

(1)本研究所建構之肝癌危險預測模型，其預測力相當佳，作業接受曲線下的面積達 0.89 (95% CI: 0.85-0.93)。

(2)以危險分層為邀請基礎之超音波肝癌篩檢，若再加上 30%順從率之抗病毒藥物治療，經八年追蹤觀察與模擬控制組相較，可避免 60%肝癌死亡率(RR=0.39, 95% CI: 0.32-0.46)。

(3)藉由與模擬控制組相較之模擬結果，僅考量抗病毒藥物使用之順從率在 30%時，可貢獻約 22%之肝癌死亡避免，若順從率提高至 50%及 70%時，避免肝

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癌死亡之貢獻可分別增加至 30%至 35%。

(4)藉由與模擬控制組相較之模擬結果，若將中風險族群超音波篩檢涵蓋率自 25%增加至 75%時，避免肝癌死亡之貢獻僅能多增加 3%。

(5)本研究經濟決策模式結果顯示，與模擬控制組相較，運用超音波進行肝癌篩檢，每挽救一個人年命，其增加成本效果比為美金 22,849 元，除超音波篩外，若再增加 30%順從率之抗病毒藥物治療，每挽救一個人年命，其增加成本效果比為美金 101,849 元，若抗病毒藥物治療順從率分別提高至 50%及 70%時，每挽救一個人年命，其增加成本效果比則分別為美金 141,805 及 181,919 元。

結論　本論文以彰化縣腹部超音波肝癌篩檢實證資料驗證使用電腦模擬建構對照組評估族群肝癌篩檢效益的效度及可行性，進一步將此設計結合肝癌疾病自然史及實證資料發展出的預測模式及存活資料，進行腹部超音波結合抗病毒藥物療法之效益評估與成本效益分析。

關鍵字：腹部超音波、抗病毒藥物、電腦模擬、效益、肝癌

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Chapter 1 Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death in Taiwan. It accounted for 8258 deaths in 2015. Annual incidence rate is approximately 48.61 per 100,000 in 2015. Although Hepatitis B vaccination implemented in a nation-wide scale may result in a decline of incidence of HCC, subjects aged 40 years or older who are not covered by vaccination program are still susceptible to the risk for developing HCC. Recently, the advances in antiviral medications, including entecavir (Baraclude), tenofovir (Viread), lamivudine (Epivir), adefovir (Hepsera) and telbivudine (Tyzeka) and interferon provide an opportunity to reduce hepatocellular carcinoma. It may reduce the attributable proportion of hepatitis virus B and C for HCC in the future. In order to provide the personalized prevention strategy for HCC in the new era, a predictive model composed of factors other than hepatitis virus infection, such as diabetes, platelet count, lipid profile, and life styles, is therefore required. Invitation by using risk groups is therefore imperative for the implementation of community-based screening for HCC.

In contrast to evaluation of the efficacy on mass screening for HCC with abdominal ultrasound by using the empirical data making allowance for selection bias based on intention-to-treat analysis, the availability of the comparator for such a preventive strategy is difficult but indispensable. To solve this issue, the main

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objective of this thesis is to create a pseudo control group by making use of information on disease natural history of HCC and to compare HCC deaths in the absence of screening by using abdominal ultrasound screening (AUS).

The objectives of this thesis are to

(1) develop a predictive model based on viral and non-viral factors for the risk of HCC;

(2) develop a natural history model for the disease progression of HCC embedded with the risk prediction model developed in (1) and the prognosis model in relation to the survival of HCC in order to form a pseudo-control group in the absence of AUS screening;

(3) estimate long-term effectiveness and cost-effectiveness of AUS in reducing HCC mortality based on the pseudo-control group;

(4) estimate long-term effectiveness and cost-effectiveness of AUS and anti-viral therapy in reducing HCC mortality based on the pseudo-control group;

(5) estimate long-term effectiveness and cost-effectiveness of AUS and anti-viral therapy in reducing HCC mortality by risk groups based on the pseudo-control group;

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Chapter 2 Literature Review

2.1 Factors affecting progression to cirrhosis

2.1.1 Smoking exposure

In 2013, Dam et al. conducted the Danish general population to explore the risk of smoking on liver cirrhosis. The smoking status were collected by multiple consecutive survey in 1976–78, 1981–83, 1991–94 and 2001–03 with long-term follow-up design. Both alcohol and non-alcohol liver cirrhosis (LC) were defined as observational endpoint. Based on the Copenhagen City Heart Study, there were 9889 women and 8790 men were recruited as study subjects and 225 and 431 liver cirrhosis cases were identified as alcohol and non-alcohol, respectively after 20.9 years of mean follow-up. Besides the alcohol and smoking behaviors, the personal characteristics and BMI were also collected for covariate adjustment. Compared with never smoking, the risk of being liver cirrhosis significantly increased by smoking exposed quantity regardless alcohol or non-alcohol liver cirrhosis, male or female after adjustment for age, educational level, BMI, and alcohol intake type (Dam et al., 2013). The viral hepatitis infection is the crucial factor for liver cirrhosis and HCC, however, the study based on Nordic country did not took the hepatitis into account due to low hepatitis, but which could not reveal whether the interaction effect between smoking and viral hepatitis on LC or HCC. The information on alcohol types,

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quantity, and frequency of alcohol consumption were collected from questionnaire. The risk of being alcoholic LC strikingly increased with increasing alcohol consumption.

In Taiwan, Yu et al. conducted the HBV carriers who followed-up by 6-month interval on Chang Gung Hospital Liver Units between 1980 and 1990. The life-style factors and biochemical markers also systematically collected from this cohort. The risk factors on LC and HCC have been reported from this cohort after follow-up with average 7.1 years. For the factors affecting on LC, those who of having fluctuating (adjusted RR=16.2), persistently elevated AFP (aRR=130.07) compared with consistent normal AFP and LC (aRR=11.77) were tend to being HCC incidence. On the other hand, the factors affecting of being LC, those subjects of having HBeAg positive (aRR=1.73), elevated ALT/AST ratio (aRR=3.69), heavy smoking (>=20 cigarette/per day) (aRR=2.13), and lower educational level (aRR=2.33) had significant higher risk of being HCC. Using the stratification approach for interaction discovery, the cigarette smoking and alcohol drinking interacted with each other. Among the subjects having habitual alcohol drinking, the heavy smoker with >=20 cigarette/ per day had highest risk of being LC compared with nonsmokers, the adjusted RR was 9.30 (95%CI: 1.10, 78.81), but this result did not apply in non-

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drinkers (Yu et al., 1997). Besides the HBV infection, the alcohol drinking and cigarette smoking played the modified factors on the risk of being LC.

2.1.2 Alcohol consumption

Alcohol is the main factors for LC and HCC regardless high or low incidence rate LC/HCC and prevalence rate of hepatitis. Based on Diet, Cancer, and Health study in Denmark, Askgaard et al. conducted this prospective cohort with 55917 participants after median follow-up time of 14.9-year and identified 257 and 85 alcoholic LC incident cases for men and women, respectively. The risk of being alcoholic LC strongly increased with elevated alcohol consumption, especially on men. Compared with 2-4 drinking days/per week, the adjusted hazard ratios (HRs) were 1.43(95%CI: 0.84, 4.67) and 3.65(95%CI: 2.39, 5.55) for 5-6 and 7 drinking days/per week in men after adjustment for age, education level, smoking status, waist circumference, and alcohol amount. The similar findings were reported on women but with slight low risk (Askgaard et al., 2015). This study demonstrated the alcohol drinking frequency by day was associated with the risk of incident LC after considering the alcohol amount.

The systemic review and meta-analysis for risk of alcohol consumption on liver cirrhosis morbidity/mortality based on three case-control studies and 14 cohorts was

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reported by Rehm et al. in 2010. The alcohol consumption was calculated by grams/per day and the association between alcohol consumption and LC morbidity and mortality was demonstrated with strong dose-response relationship, regardless gender. Using the random effect model,

John and Hanke published the study and pointed out the effect of alcohol and tobacco consumption on the LC mortality with 62-year follow-up using the trend analysis in Germany from 1952 to 2013. The annual mortality rate of LC and amounts of alcohol and tobacco were collected from National Statistics Office. The LC mortality rate increased from 1952 to 1970 then started to decline since 1978 that was similar trend of amounts of alcohol and tobacco sales, especially on the trend of men. This phenomenon indicated that reduction in both alcohol and tobacco consumption were associated with decreasing on LC mortality. Although both alcohol and tobacco are defined as important factors on LC and HCC, but this study demonstrated the long-term ecological association to support this evidence, especially on the high alcohol consumption country (John and Hanke, 2015).

It is challenge that the risk factor for HCC incidence among those who were without viral hepatitis infection. In 2015, the hospital-based retrospective cohort study was proposed from Seoul National University Hospital based on 6661healthy subjects with median follow-up time of 6.2 years. Using the fibrosis indices (FIB-4) to

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quantify the level of liver fibrosis, the risk of HCC incidence was significantly increased by FIB-4 value, especially for those who having heavy alcohol drinking. This study reported the heavy alcohol drinking would influence the HCC incidence and the impact must increases by FIB-4 fibrosis situation (Suh B, et al., 2015).

2.1.3 Metabolic factor and fatty liver

Jan et al. conducted the Keelung Community-based Integrated Screening (KCIS) to investigate the association between chronic diseases and hepatitis. For the hepatitis B virus infection, the significant inverse association between HBV and fasting glucose, blood pressure, HDL, TG, was noted, but the positive association was found for anti-HCV except TG (Jan CF et al., 2006). Following the previous study, in 2007, Lai et al. conducted the prospective cohort of 54979 subjects who attended the KCIS program between 1999 and 2002, then followed-up to the end of 2003. This study explored the risk factors for HCC based on hepatitis status of chronic diseases (hypertension, DM, hyperlipidemia) and life-style. After adjustment for hepatitis, smoking, and drinking, the Type2 DM showed the significant effect on HCC. The further analysis also demonstrated the DM effect was modified by HCV and cholesterol level. The result indicated that DM was significantly associated with HCC incidence for those who of being HCV negative and high level of cholesterol (Lai et

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al., 2007). In 2012, Ko et al. also carried out the hospital-based case-control study design to discuss this issue as well. Using the retrospective case-control study design, the DM, hepatitis, and other information were retrieved from medical chart. Among the 369 HCC cases and 1536 controls, the DM shows the significant higher risk on HCC in HCV negative and also demonstrated synergistic effect with HBV. (Ko WH, et al., 2012).

The prevalence rate of Nonalcoholic fatty liver disease (NAFLD) is dramatically increasing in the world, which is highly associated with increase in metabolic syndrome. The NAFLD is widely range of nonalcoholic fatty liver (NAFL), steatohepatitis (NASH), and liver cirrhosis. In 2017, Kabbany et al. conducted the National Health and Nutrition Examination Survey (NHANES) data with two periods 1999-2002 and 2009-2012 to discuss the risk of being serve fibrosis or liver cirrhosis and revealed that the trend of liver cirrhosis or advanced liver fibrosis. Compared with 1999-2002, the results rates of NASH cirrhosis and NAFLD-associated advanced fibrosis increased 2.5-time and 2.0-time, respectively in 2009-2012. In the same period, those metabolic factors also significantly increased in obesity, diabetes, .and insulin resistance (Kabbany, et al., 2017). Based on these results, we can expect that the chronic liver disease and cirrhosis will play the important role of prevention on liver diseases, even the viral hepatitis has been gradually overcome.

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In 2018, Wong et al. conducted the retrospective cohort with 8-year follow-up to discover the metabolic syndrome factors increase the HCC risk based on HCV with LC Hispanic patients. Their results demonstrated that metabolic syndrome factors>=2 was significantly associated with HCC and decompensation, this result was strongly shown on the Hispanic population compared with other. This finding supported that metabolic syndrome and components as import risk factors for HCC, especially for HCV (Wong, et al., 2018).

2.1.4. Hepatitis B virus (HBV) infection

The HBV carriers can be classified into active and inactive carriers. In 2006, Iloeje et al. conducted the Taiwanese cohort with untreated HBV patients. The baseline biomarker and serum have been stored the first entrance and the baseline HBV DNA titer was also performed. This result reported that the risk of being LC increased with HBV DNA titer, the higher titer and higher incidence of LC. Compared with undetected subjects, the adjusted relative risk (RR) of being were 1.4, 2.5, 5.9, and 9.8 for titers of 300-9.9*10^3, 1-9.9*10^4, 1-9.9*10^5, and 1.0*10^6 copies/mL, respectively after adjustment for age, gender, alcohol drinking, and cigarette smoking. This phenomenon of HBV DNA titer for LC prediction dominated among HBeAg negative with ALT normal level. The adjusted RR of being were

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2.1(95%CI:1.1, 4.0), 3.7(95%CI:2.0, 7.1), 10.4(95%CI:5.6, 19.6), and 12.3(95%CI:6.1, 25.1) for titers respectively, compared with undetected subjects (Iloeje et al., 2006). These results indicated that HBV DNA can strongly predict the risk of LC, especially for those who of being healthy HBV carriers with normal ALT.

The prevalence of HBV infection is higher in Taiwan since the birth cohort elder than 1980 due to vertical transition from parents' HBV carriers, but dramatically reduce HBV infection rate after the universal infant vaccination program since 1984. The long-term effect on the HCC incidence reduction for children and young adults also have been reported in recent scientific paper (Chang MH, et al., 1997 & Chang MH et al., 2016).

2.1.5 Hepatitis C infection

Besides the hepatitis B virus infection, the HCV infection also plays the important role on LC and HCC development. Both hepatitis are predominant factors for HCC and LC, but the attribute is highly dependent on the prevalence rates. (de Martel C, et al., 2015). Compared with the prevalence rate of HBV infection, the HCV is more higher prevalence in western countries. In Egypt, Schiefelbein et al. employed the case-control study to explore the association and risk of HCV on HCC incidence based on cancer hospital. Among 148 HCC as cases and 148 controls, the

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anti-HCV positive rates were 89.2% and 49.3% for case and control groups. The risk of those who HCV positive that being HCC was 9.7-time (95%CI: 3.3, 28.0) compared with anti-HCV negative and HBV risk was 5.4 (95%CI: 0.9, 31.8). This result shows the higher risk of being HCC on HCV compared with HBV, especially for the high prevalence rate area of HCV (Schiefelbein E et al., 2012).

The HCV infection for HCC incidence may play the different impact by different age group. Yi et al. employed the National Health Insurance Service database to discover the risk factor for general population which recruited the health check-up aged over 30 Korean from 2002 to 2003 and followed-up to 2013. After adjustment for the age, gender, alcohol drinking frequency and quantity, the risk of HCV positive on the HCC incidence were demonstrated the HRs with 5.72(95%CI:2.55, 12.84), 5.40(95%CI:3.06, 9.51), and 11.43(95%CI:7.37, 17.72) for those age 40-49, 50-59, and 60-69, respectively. This finding showed the HCV might play the different risk by age status and this should be considered for risk prediction by different age (Yi SW et al., 2018).

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2.2 Predictive model for cirrhosis

The predictive models for Cirrhosis have developed for **general population,** patients with **chronic hepatitis B (CHB)**, and patients with **chronic hepatitis C** (CHC) (Table 2.1).

Seyed Moayed Alavian reported the main purpose of this study was to assess the risk factors that led to the development of Chronic Hepatitis B Virus patients in Iran to Cirrhosis. During the study period from 1995 to 2014, the patients were followed up for 270 patients (13 to 78 years old) with HBsAg over 6 months. The patients were from two major Iranian hospitals and were excluded on the basis of characteristics of cirrhosis, such as immunocompromised conditions, concurrent HCV, HIV infection, or other liver diseases, or the patient refused to participate in the study.

Six months after the patient's first survey, the study observers will assess the recipients and assess them once a year. The main investigations were past medical history, including whether the patient had diabetes, drinking, smoking or opiate addiction. In addition, family history of liver disease, such as HBV carrier status, chronic HBV, cirrhosis, and HCC were also documented. During each visit, the investigators performed liver function tests including serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and serum albumin,

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total bilirubin, thrombin time (PT), and fasting blood glucose (FBS), platelet counts and serological HBV markers.

The analysis methods are Univariate, multiple logistic regression and backward stepwise logistic regression. The results showed that the age of 45 years or older, HDV positivity, HBeAg negativity, a platelet count of <150 (109)/L, and an HBV DNA level of≧2,000 IU/mL are significant, and they are risk predictors of liver cirrhosis.

These 5 predictors can be obtained by simple methods and may be used for simple screening to assess the risk of cirrhosis.

2.3 Predictive model for HCC among cirrhosis patients

Cirrhosis is one of the major risk factor for HCC development. The prognosis of cirrhosis depends on the both the underlying cause and treatment. The risk of developing HCC in cirrhosis includes HCV cirrhosis, chronic HBV infection, hemochromatosis, alcoholic cirrhosis, and biliary cirrhosis. (Fattovich et al, 2004; Schuppan & Afdhal, 2008; Mancebo et al., 2013; EI-Serag et al., 2014;)

Multiple clinical-based scoring systems with non-invasive and invasive clinical markers have been proposed to predict HCC development in subjects with cirrhosis (Table 2.2). Ganne-Carrie et al carried out a prospective cohort study to identify the risk of HCC among 151 patients with cirrhosis from 1987 to 1990 and followed-up

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until 1994. 31 HCCs were found with median follow-up time of 51 months. Total of 22 predictive variables at enrollment for HCC occurrence were assessed. The predictive factors were age>=50, male, large esophageal varices, prothrombin activity <70%, AFP>15ng/L, and anti-HCV antibodies for HCC occurrence. (Ganne-Carrie et al., 1996). However, the model validation in this study has not been carried out based on small sample size.

Another prospective analysis of risk factors for HCC in patients with liver cirrhosis was also conducted in Spain in 2003. The predictive ability for different risk factors was evaluated using Cox regression model based on a total of 463 patients with liver cirrhosis. The study demonstrated the predictive factors for the development of HCC including age>=55, , prothrombin activity ≤75%, Platelet count $<75\times10^3/mm^3$, and anti-HCV antibodies The risk score for HCC development was generated as follows: 1.65*(prothrombin activity≤75%) + 1.41*(age≥55) + 0.92*(Platelets$<75\times10^3/mm^3$) + 0.74*(anti-HCV). The predictive model was validated by internal validation. (Vel´azquez et al., 2003).

In 2013, machine-learning algorithm, a novel methodology, was applied to improve the predictive ability in predicting development of HCC among patients with liver cirrhosis. The most important predictive variables were aspartate aminotransferase, alanine aminotransferase, the presence of ascites, bilirubin, baseline

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AFP level, and albumin in machine-learning algorithm model for HCC development. Machine-learning algorithms outperform conventional regression models in improving the accuracy of risk stratifying patients with cirrhosis. This study enrolled 442 patients with cirrhosis between 2004 and 2006. A total of 41 patients developed HCC after a median follow-up of 3.5 years. The machine algorithm has significantly better diagnostic accuracy against conventional regression analysis ($P<0.001$). (Singal et al., 2013).

A predictive model for predicting the risk of HCC development was developed by Flemming et al. in 2014 based on a large cohort of 34,932 patients with cirrhosis between 2002 and 2011.Age, diabetes, race, etiology of cirrhosis, sex, and severity of (ADRESS) liver dysfunction was identified as predictors by Cox regression analysis. The C-index of 70.5% (95%CI: 68.8%-72.2%) was estimated in the derivation cohort. The C-index was close to 70% in the interval validation cohort. The ADRESS-HCC risk prediction model has some advantages over these previous risk models, including calculating the annual incidence of HCC, statistical power under a large sample size, and a robust performance in both internal and external validation data sets. (Flemming et al., 2014).

Another risk prediction model was developed and validated in 2014 based on a large samples of 11721 patients with hepatitis C virus-related cirrhosis. A predictive

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model that included data on levels of AFP, ALT, and platelets, along with age at time of AFP test. The multivariable logistic regression models was constructed to determine the predictive ability of this AFP-adjusted model. The predictive model was validated by Hosmer-Lemeshow test.

2.4 Predictive model for patients infected with HBV

Lee et al. developed the prediction models for long-term cirrhosis and HCC based on HBV positive patients. The subjects aged 30-65 of the prospective REVEAL-HBV cohort of 23820 were collected between 1991-1992. The factors including in the prediction model were gender, age, cigarette smoking, alcohol drinking, HBeAg, ALT, HBV genotype, and level of titers of HBsAg and HBV DNA. The factors for both predictive models for LC and HCC respectively was quite similar, but with different risk. The AUROC for prediction 3-, 5-, and 10-years were 0.79, 0.80, and 0.82 for LC, but the AUROC of HCC prediction were 0.89, 0.85, and 0.86 for 5-, 10-, and 15-year, respectively (Lee MH et al., 2013). Yang et al. established HCC risk scores for HBsAg-positive patients and assesses the validity of this prediction model. Many studies have shown that chronic hepatitis B is one of the major risk factors leading to liver cirrhosis and hepatocellular carcinoma (HCC). Because previous studies about HCC risk scores for patients with chronic hepatitis B have limited the number of sample size and have

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not been externally validated. So, the most important part of this study is to establish a simple and useful predictive score to confirm the risk of developing HCC in patients with chronic hepatitis B.

Mainly divided into 2 studies cohort (development cohort and validation cohort), HBsAg-positive and anti-HCV-negative and no liver cirrhosis in development cohort and no HBV treatment during follow-up in both two groups cohort. A total of 3584 the development cohort, using community-based data from Taiwan, aged between 30 and 65 years, with a median follow-up time of 12 years (IQR 11.5-12.4), had 113 confirmed HCCs during the follow-up. The validation cohort database was collected from three independent hospitals with 1,505 individuals and the average follow-up time was 7.3 years. The first hospital was the University of Hong Kong (UHK), 820 patients aged 14 to 83 years with an average of 6.3 years of follow-up. The second hospital was the Chinese University of Hong Kong(CUHK), 426 patients aged 12 to 80 years, with an average of 9.4 years of follow-up, a third hospital with Yonsei University Hospital (YUH), 259 patients aged 24-70 years, median follow-up of 9.4 years (IQR 5.0-10.3). 111 confirmed HCC cases in validation cohort. (Yang HI, et al., 2011)

Calculating the risk score is divided into three steps. First, the cox proportional hazard model was used to calculate the beta regression coefficient, p value, hazard ratio, and 95% CI for each predictor (sex, age, serum ALT concentration, HBeAg status, and

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serum HBV DNA level (by PCR assay)). Second, using the above regression coefficient as a numerator, the 5-year group of the age regression coefficient is the denominator. The result of the division is an integer, which is the risk score of the predictor. Third, use the sum of the risk scores for each predictor (up to 17 points) to calculate the risk of developing HCC. In order to confirm the validity of the prediction model, two methods are used, one for the ROC curve and the other for the Kaplan-Meier model for HCC risk assessment.

The ROC curves of HCC risk for 3, 5 and 10 years of validation cohort are drawn using the above risk score calculation method. The three-years AUROC is 0·811 (95% CI 0·790–0·831), the 5-years AUROC is 0·796 (0·775–0·816), and the 10-years AUROC is 0·769 (0· 747–0·790). This indicates that Risk score model is acceptable discrimination. The correlation coefficient between the predicted HCC risk and the observed risk is 0·973 for 3-year risk, 0·942 for 5-year risk, and 0·994 for 10-year risk.

The risk score calculation model obtained in this study is mainly aimed at HBsAg positive cases without liver cirrhosis, but in actual community screenings, it is difficult to obtain information on whether people have cirrhosis. In addition, all the cohorts did not receive antiviral therapy during the tracking of this study, which is also less feasible in clinical practice. According to other studies, the risk of HCC in HBsAg negative and anti-HCV negative cases has increased, and is not limited to HBsAg positive cases. If

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considering the cost, the data collection of the predictors of this study, such as the detection of HBV DNA, the national health insurance payment points is 2,000 points, and it costs about NT$2,500 at its own expense, which takes a relatively high cost. Therefore, it is necessary to develop a new risk prediction model for liver diseases for community screening.

2.5 Dynamic prediction for HCC

In 2017, Wang et al., this thesis mainly discusses how to establish a personalized dynamic prediction model for HCC. Prior to this paper, there have been many studies on HCC prediction models, mostly related to HBV positive and HCV positive patients. However, recent studies have found that the incidence of HCC in addition to HBV, HCV infection, but also associated with metabolic syndrome, fatty liver disease and so on. In addition, in a variety of prediction models, calculations are based on baseline characteristics not using dynamic model analysis of repeated measurements. Therefore, the purpose of this study is to establish a dynamic prediction model for personalized HCC in the general population, and then predict the occurrence of HCC in each person.

There are 2 sources of DATABASE in this study. The first dataset was from the Keelung Community-based Integrated Screening Program. The data was collected from

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September 28, 1999 to December 31, 2009. A total of 108,434 residents aged 20 or above participated. The residents' liver cancer screening program uses a 2-stage screening model. In the first phase, collect HBsAg, anti-HCV, AST, ALT and alpha-fetoprotein (AFP) and family history of HCC to identify high-risk groups of liver cancer. In the family history of HCC, HBsAg positive, anti-HCV positive, AST ≥ 60 U/L, ALT ≥ 60 U/L, or AFP ≥ 20 ng/mL, as long as one of them is positive, it enters the second stage to Screening by using abdominal ultrasound. HCC cases were determined by screening for confirmed diagnoses or cancer registration data. The second database comes from REVEAL-HBV group. There were 3,584 patients between the ages of 30 and 65 who were HBsAg-positive or anti-HCV-negative and had no HCC and collected HBV DNA data at the time of filing. During the follow-up period, the subjects did not receive antiviral therapy and there were 244 confirmed HCC cases (Wang et al., 2017).

It has a total of 3 statistical goals. The first statistical method is the use of Bayesian clinical reasoning algorithm to establish a personal risk prediction model for HCC in order to stratify the risk of average-risk subjects and high-risk hepatitis B carriers. The second statistical method is to use the time-dependent Cox regression model to establish a dynamic risk prediction model of HCC, which uses the dynamic changes of HBV DNA and ALT in hepatitis B carrier and the covariation of average-risk subjects over time (Includes AST, ALT, AFP, AC sugar, and platelet). Thirdly, a dynamic risk score

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prediction model based on the second statistical method was used. The model was established based on the time-varying covariates of hepatitis B carrier. The categories of risk scores were used to explain the dynamics of intermediate variables and to predict HCC.

There were 484 confirmed HCCs in the community-based screening cohort, male age, infection of hepatitis B and C virus, family history, alcohol drinking, elevated ALT, AST, AC sugar, and AFP, and platelet-low both higher in HCC cases. In addition, the distribution of diagnosed HCC cases and non-HCC cases in these variables was statistically significant (<0.05). Considering the impact of time, we first used the logistic regression to calculate the age and gender impact of HCC cases in this community-based cohort. The regression coefficients for males and age (increased every 5 years) were 0.5530 and 0.2924, which were statistically significant, and the odds ratios were 1.74 and 1.34. Based on this logistic regression model, the risk of HCC prediction was calculated according to the grouping of gender and age. For example, a 57-year-old man has an HCC risk of 0.64%. According to the history-taking and biochemical examination, this male can be subdivided into different risk groups using the Bayesian clinical reasoning algorithm. According to our constructed model, the a-57-year-old man's posterior HCC risk can be corrected by 0.11. % to 70%. In HBV carrier, REVEL cohort, the adjusted hazard ratio (aHR) compared with

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HBV DNA <300 copies/mL, aHR of HBV DNA 300-9 999, 10^4-99 999, 10^5-999 999 and ≧10^6 from 1.15 (95% CI: 0.51-2.58) to 4.74 (95% CI: 2.12-10.63). The aHR with ALT ≧ 45 IU/L compared with ALT <45 IU/L was 1.66 (95% CI: 1.08-2.56). However, these aHR values are exaggerated in applying dynamic values for repeated inspections. The risk score will be derived from the multivariable time-dependent Cox model. The authors used the four-state Markov model to derive dynamic changes in HCC risk and risk score status. The progression rates ranged from low to intermediate risk of 4% (95% CI: 3.7-4.4%); intermediate to high risk was 3% (95% CI: 2.8-3.6%). In addition, the regression rates ranged from intermediate to low-risk to 6% (95% CI: 5.7-6.7%); high-to-intermediate risk was 11% (95% CI: 9.3-16%). The HCC hazard rate for the high-risk group is 2.5%. The hazard rate divided by 5.5 is the HCC hazard rate for the intermediate risk group. In addition, the HCC hazard rate of the intermediate risk group is divided by 5.8 times the HCC hazard rate of the low risk group. Divided into three groups based risk score, ≦ 10,11-14, ≧ 15, HCC cumulative mortality of 20 years were 58 cases per 1000, 103 cases and 177 cases. This 20-year cumulative mortality rate for HCC accounts for three transient states of dynamic changes in HBV DNA levels (as a function of time) and all covariates of the risk-score group.

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2.6 Cost-effectiveness analysis for HCC screening

Kuo et. Al, 2016, the purpose of this study was to evaluate the cost- effectiveness analysis of two hepatocellular carcinoma screening methods. The two screening model were a two-stage screening model and a large-scale abdominal ultrasound screening model. In order to show the natural history of liver disease who did not participate in screening, this study used four-state Markov model to construct the decision model. The authors divided the population into two groups: non-cirrhotic and cirrhotic groups. We use the Markov cohort simulation method to track this virtual cohort, tracking the period from 40 to 79 years, or until death. The time period of our Markov model is one year. The statistical method of this research mainly uses TreeAge Software to build the model, and uses Winbugs software to estimate the parameters. And according to different screening methods to construct a decision tree model.

On three different modes of HCC screening were compared: (1) no screening and invitations. This group of people is the basic control group. (2) Two-stage screening mode. In the first phase, high-risk patients were selected using blood tests. The factors were HBsAg, anti-HCV antibodies, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alpha-fetoprotein (AFP). Then in the second phase, the high-risk patients selected in the first phase of the abdominal ultrasound examination

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were used (at least one of the following outcomes: positive HBsAg or anti-HCV antibodies, AST ≥ 40 U/L, ALT ≥ 40 U/L, or AFP ≥20ng/mL). (3) Use abdominal ultrasound for large-scale screening. All residents have.For strategies 2 and 3, the screening interval is yearly (Kuo MJ, et al., 2016).

The results showed that using a large-scale abdominal ultrasound for HCC screening, the annual incremental cost-effectiveness ratio of this model is USD39825, and the annual incremental cost-effectiveness ratio of the two-stage screening model is USD 49733. Compared with the two, it was found that large-scale abdominal ultrasound screening is more cost-effective than the two-stage screening model. The first screening of the age of 50 years and the biennial screening interval was the most cost-effective.

Based on the results of this study, we can apply this result to other HCC high endemic areas for large-scale abdominal ultrasound screening, starting from the age of 50 screening, screening interval of 2 years, and conduct cost-effectiveness assessment.

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Table 2.1 The predictive model for HCC among patients with cirrhosis

Author/Year	Area	Subjects	Methods	Predictive model	Validation	Remarks
Ganne-Carrie et al 1996	France	151 Cirrhosis	Cox regression model	6*age+4*sex+3*esophageal varices +3* prothrombin activity +3*AFP+3* anti-HCV antibodies		This study predictive score, based on six common clinical and biological variables, and it is easy to calculate routinely and can provide the selection of a group of patients requiring intensive screening for HCC.
Velázquez et al., 2003	Spain	463 Cirrhosis	Cox regression model	1.65*(prothrombin activity≤75%)+1.41*(age≥55)+0.92*(Platelets<$75\times10^3/mm^3$)+0.74*(HCV)	Log-rank test(P>0./1)	
Singal et al., 2013	USA	442 patients	Cox regression model	Conventional predictive model: Baseline AFP level and Male gender Machine-learning algorithm model: AST, ALT, the presence of ascites, bilirubin, baseline AFP level, and albumin.	The C-index of the conventional predictive model was 0.64 (95% CI 0.54-0.73). The machine-learning algorithm had a c-statistic of 0.71 (95%	Machine-learning algorithms improve the accuracy of risk stratifying patients with cirrhosis.

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Author/Year	Area	Subjects	Methods	Predictive model	Validation	Remarks
					CI, 0.63-0.79)	
Flemming et al 2014	USA	17124 Cirrhosis	Cox regression model	score=0.0532*age+0.2135*Diabetes+ 0.02058*race(1= nonwhite or Hispanic)+ 0.3509* Etiology of cirrhosis (alcohol/metabolic)+1.246* Etiology of cirrhosis (viral)+0.5114*sex(1=male)+ 0.1170*Severity(CTP score (5-15)) (ADRESS-HCC model)	The C-index was 0.705 (95% CI, 0.688-0.722)	The ADRESS-HCC risk score offers significant advantages over these previous risk models, including calculating the annual incidence of HCC, statistical power under a large sample size, and a robust performance in both internal and external validation data sets.
El-Serag et al., 2014	USA	11,721 HCV patients with Cirrhosis	Logistic regression model	AFP levels, ALT, and platelets, along with age	The predictive models were validated by Hosmer-Lemeshow test(P>0.05)	6-month interval was used to predict the occurrence of HCC in AFP-based model

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Chapter 3 Materials and Methods

3.1 Population-based HCC Screening in Changhua

Design of Study on Community-based Screening for HCC with Abdominal Ultrasonography

In Changhua County, the Changhua Community-based Integrated Screening (CHCIS), which screens for liver cancer and other neoplastic diseases (breast cancer, colorectal cancer, oral cancer, and cervical cancer) and non-neoplastic diseases (hyperlipidaemia, hypertension, and hyperglycaemia) was launched since 2005. The details of program design and implementation have been described elsewhere (Chen et al, 2004; Chiu et al, 2006). As Changhua county is one of counties with high incidence of HCC, the two-stage screening program for HCC under the CHCIS program was considered in the periods between 2005 and 2008. The two-stage screening for HCC has been describe in details elsewhere (Chen et al., 2012). In brief, subjects who has one of the following criteria: (1) positive for hepatitis B surface antigen (HBsAg) (2) positive for anti-hepatitis C virus (HCV) antibody (3) high alpha-fetoprotein (≥20 ng/mL) (4) high AST (≥45 IU/L) (5)high ALT (≥45 IU/L) levels were referred for ultrasonography as confirmatory exam in hospitals or clinics.

However, screening for high risk individuals might not be sufficient in high

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incidence area. From 2008 onward, the Changhua county government launched an outreach ultrasonography screening program for residents aged 45–69 years, which was not limited to those within the high-risk group as defined by the two-stage screening program mentioned above in order to control disease on a population scale. The details of this mass screening for HCC with abdomen ultrasound were given elsewhere (Yeh et al, 2010). In brief, a phased-in method was adopted to invite eligible candidates for screening by the application of a risk-score-guided program. We used information on significant biomarkers generated from the first stage of the CHCIS screening program, including positive tests for HBsAg or anti-HCV and high alpha-fetoprotein, AST, or ALT levels, as well as low platelet counts or type 2 diabetes, both of which are significant risk factors for HCC (Lai et al, 2006; Lu et al, 2006). To enhance access to abdominal ultrasonography by community residents, based on the risk-score-guided invitation, the eligible residents were invited to the local health centre to undergo abdominal ultrasonography performed by gastroenterologists.

Risk-score-guided Invitation

Individual information on age, gender, elevated AST, ALT, and AFP, positive HBsAg and anti-HCV, type 2 diabetes, and low platelet levels were used to generate

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as risk score for invitation (Figure 3.1). Basically, the risk score was established by HCC prediction. The risk score for predicting HCC was derived using empirical data from the Keelung community-based integrated screening program, the first multiple screening program in Taiwan, which was conducted 5 years earlier than the CHCIS program.

Because positive HBsAg and anti-HCV are two dominant risk factors for HCC, we classified the eligible subjects into two groups, Group A: subjects with HBsAg positive or anti-HCV positive and Group B: subjects with free of these two hepatitis virus infections. In each group, the risk score was reckoned by using time-invariant variables including age, gender, results of biochemical tests, and diabetes mellitus and time-dependent biomarkers such as AST, ALT, AFP, and platelets, the most recent results were used. The risk scores for the two groups were generated by the following formulas:

Risk score for Group A = -9.1940 + 0.0474 × Age + 1.2878 × (Male) + 2.8922 × (AFP ≥20 ng/mL) + 1.1934 × (AST ≥45 IU/L) + 1.3033 × (Platelet count <150 × 10^3)

Risk score for Group B= -11.7821 + 0.0358 × Age + 1.3580 × (Male) + 1.4340 × (type 2 diabetes) + 1.3124 × (ALT ≥45 IU/L) + 2.0298 × (Platelet count <150 × 10^3)

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The risk scores were delivered to public health nurses for invitation of all eligible subjects, along with the priority of their individual invitation to undergo abdominal ultrasonography. In Group A, the subjects were considered as extremely high-risk individuals if their scores were above or equal to the median risk score of Group A. In contrast, high-risk individuals were those who have scores below the median risk score in Group A. Those risks in Group B were classified as intermediate-risk individuals based on scores above or equal to the third quartile of the risk score. Low-risk individuals were those scores below the third quartile of the risk score in Group B.

Invitation with Phase-in approach

Based on the risk score calculation above, the subjects were invited to attend abdominal ultrasonography by prioritising invitations. In the first period between Oct. 2008 and Jan. 2009, the eligible population for invitation was derived from those attending the CHCIS program during the screening period between 2005 and 2007. There are 26 townships in Changhua County. In each township, the invited subjects of around 60 patients with the highest score in each town were selected and screened within an interval of 2–4 weeks between Oct. 2008 and Jan. 2009. During the second period between Feb. 2009 and Mar. 2009, the eligible population for invitation was derived from attendees of CHCIS in 2008. In each township, the invitation list was

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selected from the highest 40 scores and the highest 41–90 scores. In the third period between Apr. 2009 and Dec. 2013, invitations were targeted to all subjects from group A because group B had cases with lower risk of HCC. In the fourth period, after Jan. 2014, invitations were selected all subjects from group A, and one-tenth of the IM groups were randomly selected, and one-thirtieth of the L group was randomly selected.

Clinical Surveillance

Subjects with abnormal findings or suspected cases of HCC from ultrasonography screening were referred to medical centres or regional hospitals to have further confirmation of HCC. HCC cases were diagnosed by MRI or pathologic confirmation with biopsy. In addition to HCC cases, other referred cases were recommended to undergo periodically clinical surveillance. The different surveillance intervals using ultrasonography were determined by clinical committees which has formed by Changhua County Public Health Bureau. Figure 3.1show the protocol of HCC screening program with ultrasonography in Changhua County.

3.2 Predictive model with logistic regression

The univariate logistic regression model was first used for identifying risk factors for outcomes of interests (liver cirrhosis/HCC and HCC) with consideration of

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age and gender. The multi-variable logistic regression model was further performed to incorporate significant risk factors identified from univariate analyses. The role of effect modifiers such as type 2 diabetes in association with HBV and HCV was tested. The odds ratios (OR) and the associated 95% confidence intervals (CI) were also reported.

The summation of products of regression coefficients in the final model and their associated value of covariates was treated as risk score for the outcomes. The regression coefficients of covariates can be considered as clinical weights for the contribution of covariates to the risk of HCC. The estimated probability of HCC for each subject according to his/her specific risk profile, i.e. the value of covariates can be calculated based on the Breslow (1972) estimator. Given different cut-off values for the estimated probability for predicting HCC, we had a series of sensitivity and specificity of our predictive model. Receiver operating characteristic (ROC) curve in the form of a plot of sensitivity by one minus specificity is presented for the performance of the predictive model. The area under ROC curve (AUC) was computed.

All hypothesis tests were two-sided taking alpha-level of 5% as the threshold of statistical significance. Statistical package software SAS version 9.4 was use for conducting analyses throughout this study.

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3.3 Multi-state predictive model

We develop a four-state progressive model to depict the disease process from free of HCC (normal, stat 1), liver cirrhosis (state 2), preclinical HCC (state 3), to clinical HCC (state 4). The progressive process for the development of HCC based on the fined states is thus depicted as follows.

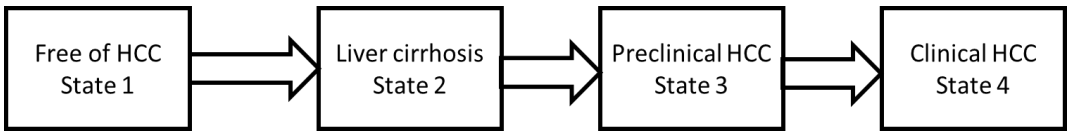

Figure 3.3.1 Multistate progressive model for HCC.

Let random variable $X(t)$ denote the state of disease progression at time t, $X(t) \in \Omega$, $\Omega=\{1,2,3,4\}$. The transition rate matrix of homogenous disease progression is thus specified as follows

$$\mathbf{Q} = \begin{array}{c} \\ \textit{Free of HCC} \\ \textit{LC} \\ \text{Pr}\textit{eclinical HCC} \\ \textit{clinical HCC} \end{array} \begin{array}{c} \begin{array}{cccc} \textit{Free of HCC} & \textit{LC} & \textit{preclinical HCC} & \textit{clinical HCC} \end{array} \\ \begin{bmatrix} -\lambda_1 & \lambda_1 & 0 & 0 \\ 0 & -\lambda_2 & \lambda_2 & 0 \\ 0 & 0 & -\lambda_3 & \lambda_3 \\ 0 & 0 & 0 & 0 \end{bmatrix} \end{array} \quad (3\text{-}1)$$

The parameter λ_1 corresponds to the incidence rate of LC, with the rate of progression to preclinical HCC at the rate of λ_2. The parameter λ_3 represents of force of surfacing to clinical stage among the subject with preclinical HCC. Let the transition probability

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matrix denoted by **P**(t) for the progression of HCC specified above. By using the Kolmogorov equation, the transition probability matrix can be derived by

$$d\boldsymbol{P}(t) = \boldsymbol{P}(t)\boldsymbol{Q}. \qquad (3\text{-}2)$$

The corresponding transition probability matrix dominate the progression of HCC is thus

$$\mathbf{P}(t) = \begin{array}{c} \\ \textit{Free of HCC} \\ \textit{LC} \\ \text{Pr}\textit{eclinical HCC} \\ \textit{clinical HCC} \end{array} \begin{array}{c} \begin{array}{cccc} \textit{Free of HCC} & \textit{LC} & \textit{preclinical HCC} & \textit{clinical HCC} \end{array} \\ \begin{bmatrix} P_{11}(t) & P_{12}(t) & P_{13}(t) & P_{14}(t) \\ 0 & P_{22}(t) & P_{23}(t) & P_{24}(t) \\ 0 & 0 & P_{33}(t) & P_{34}(t) \\ 0 & 0 & 0 & 1 \end{bmatrix} \end{array} \qquad (3\text{-}3)$$

Let the covariates including the demographic characteristics such as sex and the laboratory examination including AFP and the status of immune response of HBV and HCV for subject *i* denoted by vector $\mathbf{z}_i$, $\mathbf{z}_i = \{z_1, z_1, \ldots, z_p\}$.The effect of these covariates on the rate at the states of disease progression can be incorporated as follows

$$\lambda_{ji} = \lambda_{j0}\psi(\mathbf{x}_{ji}),\ j=1,2,3,4 \quad , \qquad (3\text{-}4)$$

where *j* represents the states of HCC progression defied as above and λ_{j0} is the baseline progression rate on the development of HCC. By using the appropriate link function denoted by $\psi(\square)$ these effect of covariates can be incorporated. One of the often used link is exponential function which give the natural interpretation of

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exponent of the estimated regression coefficient as the ratio of hazard. By using the exponential function, formula (3-4) is thus

$$\lambda_{ji} = \lambda_{j0}\exp(\mathbf{x}_{ji}\boldsymbol{\beta}_j), \quad (3\text{-}5)$$

where the effect of the covariates on the progression of HCC at each *j* state captured by the regression coefficient $\boldsymbol{\beta}_j$.

Based on the estimated results derived from the constructed four state Markov model for HCC progression specified as above, the control group, namely the evolution of HCC without AUS screening programme, can be projected using estimated results derived from the empirical data of the population of the target of our programme. For the further consideration of the heterogeneity of our population in terms sex and the proportion of subjects with viral hepatitis, the corresponding model incorporating the effect of covariates on each states of HCC progression was utilized for the derivation of the projected control group.

3.4 Markov Decision Analysis

A Markov decision tree model was framed with three scenarios: mass screening with abdominal ultrasonography, mass screening with abdominal ultrasonography plus anti-viral therapy, and pseudo control (natural history model). The simulated cohort was divided into four risk groups: extremely high risk, high risk, intermediate

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risk, and low risk groups. In these groups, study samples would be randomly allocated into intervention and pseudo control group.

In the decision tree (see Figure 3.2), the symbol of □ was defined as decision node which indicates the different scenarios or decision strategies. The symbol of ○ was defined as chance node to demonstrate the chance event in certain probability. We used Markov node (M) to represent the yearly dynamic change of disease status. The four-state natural history of HCC was illustrated by normal, non-liver cirrhosis, liver cirrhosis, and HCC. Among those with intervention, the disease progress will follow natural history but different transition probabilities would be assigned. The final states with HCC cases or HCC deaths was defined as terminal node (◁) after simulation.

A Markov cycle tree with a cycle length in a year was adopted to simulate HCC process for each subject from 45 to 74 years of age. Transition probabilities between different disease statuses were derived from literatures. Monte Carlo simulation is applied to select values at random from specific distributions for assigned parameters. Under the scenario of screening with ant-viral therapies, the efficacy of anti-viral therapy would be assigned in treatment node after screening. The node with anti-viral therapies would be followed by different outcomes on HCC progress in simulated cohort.

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3.5 Cost-effectiveness analysis

Our cost-effectiveness analysis was conducted from a societal perspective. The effectiveness of intervention program was converted by the life-year gained. The direct costs for screening, confirmatory exams, anti-viral therapy, and treatment on HCC were collected and mainly derived from national health insurance claim data. The indirect costs were derived from the production loss. The discount rate was assigned as 3%. The incremental cost-effectiveness ratios (ICER) are presented for comparison between different preventive strategies.

The use of parameters as base cases in cost-effectiveness are listed in Table 3.1.

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Table 3.1 Parameters for Base-case Estimates

Variables	Base-case	Reference
Disease Natural history		
Prevalence of cirrhosis	1.77%	Yang et al., 1999
Annual transition rates from Preclinical HCC to Clinical HCC (per year)		
For Non-cirrhosis	0.376	Chen et al., 2002; Yu et al., 2004
For Cirrhosis	0.637	Chen et al., 2002; Yu et al., 2004
HCC with non-cirrhosis to HCC death	0.7769	
HCC with cirrhosis to HCC death	0.5769	
Survival rate of surveillance-detected preclinical HCC	0.75	Yu et al., 2004
Sensitivity to Cirrhosis	0.80	Kuo et al., 2007
Sensitivity to HCC	0.95	Chen et al., 1999
Specificity to HCC	0.70	Chen et al., 1999
Direct cost (USD)		
Ultrasonography	26	BNHI
Confirmation (USD)		
Triple–phase abdominal CT	148	BNHI
Ultrasonic guidance for biopsy	38.3	BNHI
Liver puncture	36	BNHI
Specimen examinations of pathology	51.2	BNHI
Treatment (USD)		
Anti-viral therapy for Hepatitis B carrier (per year)	1776	BNHI
Anti-viral therapy for Hepatitis C	8333	BNHI

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Variables	Base-case	Reference
carrier		
Initial cost of HCC treatment	4892	NTUH
Continuing care cost of HCC treatment	4266	NTUH
Incurable-cancer care (average)	5691	NTUH
Indirect cost (USD)		
Screening time (hour)	0.5	Wu et al., 1998; Chen et al., 2002
Person accompanied for screening	0	Wu et al., 1998; Chen et al., 2002
Time spending for ultrasonography	4	Wu et al., 1998; Chen et al., 2002
Confirmation time (hour)	8	NTUH; Wu et al., 1998
Person accompanied for confirmation	1	NTUH; Wu et al., 1998
Inpatient hospitalization (day)	15	NTUH
Inpatient recovered at home (day)	15	Wu et al., 1998
Person accompanied for inpatient care	1.69	Wu et al., 1998
Outpatient time per visit (hour)	4	Wu et al., 1998
Outpatient visit per year	9.7	NTUH
Patient accompanied for outpatient visit	0.77	Wu et al., 1998
Inpatient of terminal care (day)	30	NTUH
Person accompanied for terminal care	1	Wu et al., 1998
Average work per month (hour)	184	DGBAS
Production value per hour (USD)	7.6	DGBAS
Discount rate (%)	3	

HCC: hepatocellular carcinoma; CT: computed tomography; BNHI: Bureau of the National Health Insurance; NTUH: National Taiwan University Hospital; DGBAS:

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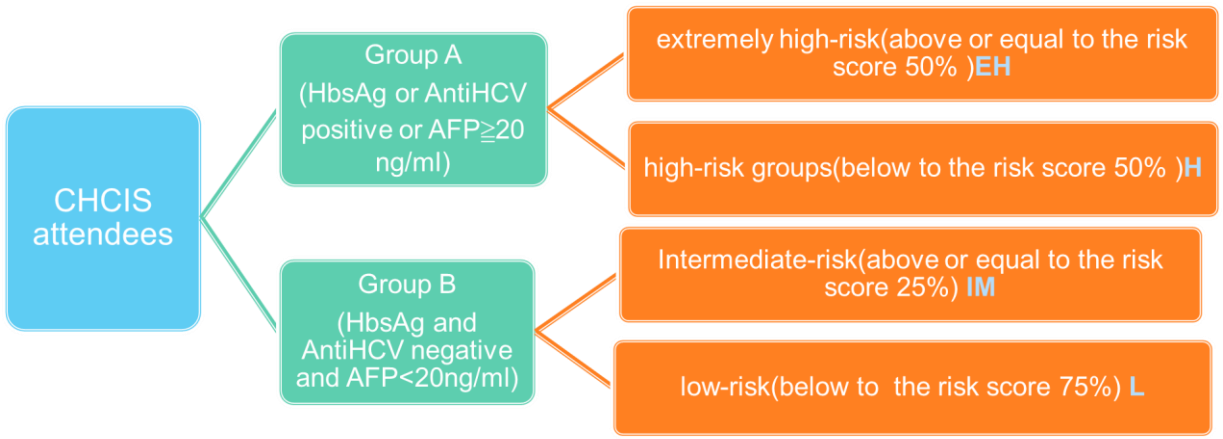
Figure 3.1 The risk stratification for the invitation in the ultrasound screening in Changhua



Risk score for Group A=-9.1940+0.0474 x Age+1.2878 x (Male)+2.8922 x (AFP≧20 ng/ml)+1.1934 x (AST≧45 IU/L)+1.3033 x (Platelet count<150 x 10^3)

Risk score for Group B=-11.7821+0.0358 x Age+1.3580 x (Male)+1.4340 x (type 2 diabetes) +1. 3124 x (ALT≧45 IU/L)+2.0298 x (Platelet count<150 x 10^3)

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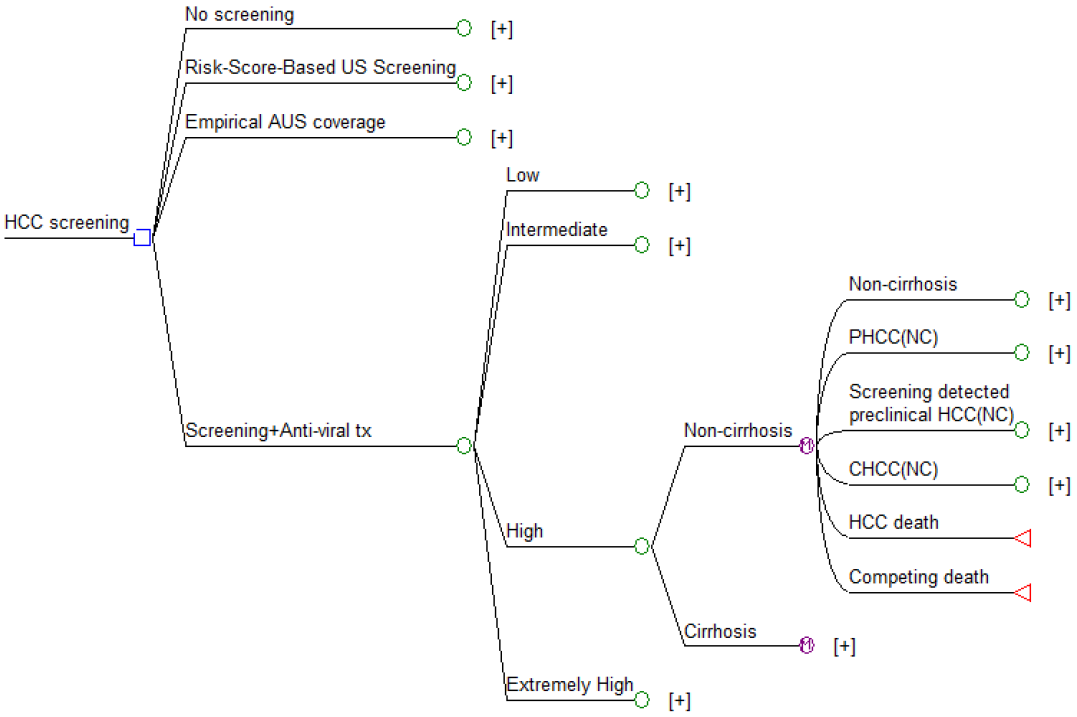
Figure 3.2 Markov decision tree for HCC screening



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Chapter 4 Results

4.1 Invitation and Attendance to the Changhua community-based AUS screening program

A total of 85,147 subjects aged 45-74 years attended the Changhua community-based integrated screening (CHCIS) in 2005-2017. All of them were classified into four risk groups (extremely high (EH)-, high (H)-, intermediate (IM)-, and low (L)-risk groups) according to the risk score used in CHCIS. Among them, 9.9% (=8430/85147) were in the EH group, 8.0% (=6816/85147) were in the H group, 23.5% (=19991/85147) in the IM group, and 58.6% (=49910/85147) were in the L group.

Following the risk score-guided invitation scheme, 20,892 eligible subjects were invited for abdominal ultrasonography screening (AUS), covering 24.5% subjects. The invitation rate was highest in the EH (96.2%) and the H (96.15), followed by IM (25.12%) and L (2.4%). The invitation rate was similar across age groups in the given group (Table 4.2).

Before the end of 2017, there was 15,957 subjects underwent AUS, with the overall attendance rate for AUS as 76.38% (=15957/20892). The attendance rate was highest in the EH group (79%), followed by H (77%), IM (74.47%), and L (63%). In

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all the four groups, the attendance rate increased with age. (Table 4.3)

The flow chart from recruitment to invitation and attendance to the AUS in CHCIS in Figure 4.1.

4.2 Findings from the screening.

Table 4.4 shows the clinical findings of AUS by risk groups. There were a total of 35,954 ultrasound examinations performed in this community-based ultrasonography screening. The detection rates for HCC (per 1,000) decreased from 4.2 for the extremely high-risk group to 0.3 for the high-risk group and 0.5 for the intermediate-risk and 0 for the low-risk group. The detection rate for liver cirrhosis was 57.2 per 1000 in the extremely high-risk group. The second high detection rate group for liver cirrhosis was the intermediate-risk group (13.5 per 1000), which was higher than the high risk group (5.9 per 1000) and the low-risk group (2.5 per 1000). The extremely high risk group also had the highest detection rate for liver nodule (44 per 1000), whereas the figure was similar in the other three risk groups (19-22%). The liver hemangioma seems equally common seen in the extremely high-, high-, and intermediate-risk groups (43-55 per 1000), and lower in the low-risk group (24 per 1000). The detection of liver parenchymal disease decreased from the extremely high-risk group (27%), to the high-risk group (19%), the intermediate-risk group (11%),

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and the low-risk group (6.5%).

We further turned the data on repeated examinations into individual-based data. The prevalence of liver cirrhosis and hepatocellular cancer by using data from the prevalent screen was 15.8 and 2.3 per 1000, respectively (Table 4.5). Both figures decreases from the extremely high-risk group to the low-risk group. The prevalence of liver cirrhosis in the EH, H, IM, and L was 32.7, 4.7, 4.0, and 2.6 per 1000, respectively. The corresponding figure for HCC was 5.2, 0.6, 0.3, and 0, respectively. Men had higher prevalence (17.7 per 1000) than female (13.8 per 1000). In both sex, the prevalence of liver cirrhosis increased from 45-49 years to 60-64 years, and decreased afterwards.

The prevalence of hepatocellular carcinoma was 2.3 per 1000 in our participants. The majority was from the extremely high risk group (34 HCCs, 5.2 per 1000). There were 21 men and 15 female patients were identified and confirmed as HCC in the prevalent screen, resulting the prevalence as 2.8 and 1.7 per 1000 in men and female, respectively.

Table 4.6 shows the incidence of liver cirrhosis and HCC in the follow-up screens. The incidence of liver cirrhosis and HCC was 491 and 39 per 100,000, respectively. Incidence of liver cirrhosis was highest in the extremely high-risk group (1047 per 100,000). The counterpart figures were similar in the other three risk groups

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(127, 134, and 126 in the H, IM, and L group, respectively). Male had a higher incidence of liver cirrhosis (626 per 100,000) than female (384 per 100,000). Similar to the trend across age groups found in the prevalence of liver cirrhosis, the incidence of liver cirrhosis increased from 45-49 years to 60-64 years, and decreased afterwards, in both sex.

As far as the incidence of HCC was concerned, the overall incidence of HCC was 123 per 100,000. There were 35, 1, and 3 incident HCCs were diagnosed in the subsequent screens in the EH, H, and IM group, respectively. The incidence in the extremely high-risk group was 272 per 100,000. Due to the sparse number of incident HCCs in the other three risk groups, the trend was not obvious seen. Men (18 incident HCCs) had higher incidence (128 per 100,000) than female (21 incident HCCs, 120 per 1000). In both sex, the incidence of HCC increased with age, except a dint in subjects aged 70-79 years in men.

4.3 The predictive model with logistic regression for HCC/liver cirrhosis

Table 4.7 shows the estimated results of univariate logistic regression model for HCC or liver cirrhosis with adjustment for age and sex. Male had higher risk for HCC/liver cirrhosis (OR=1.4, 95% CI 1.1-1.7). Compared to those younger than 55 years old, subjects in the age groups of 55-64 (OR=1.53, 95% CI: 1.25-1.88) and elder than 65 years (OR=1.31, 95% CI: 0.99-1.72) had higher risk of HCC/liver

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cirrhosis. Among all other risk factors, elevated AFP level (higher than 20 ng/mL) has the highest crude odds ratio (OR) (22.8, 95% CI: 15.6-33.4), followed by the low platelet count (OR=9.7, 95% CI: 8.0-11.8), elevated GOT (OR=7.7, 95% CI: 6.4-9.4), and elevated GPT (OR=4.1, 95% CI: 3.4-5.0). For the hepatitis virus infection, the OR for both HBV and HCV positive, HCV infected only, and HBV infected only was 12 (95% CI: 6.5-21), 14 (95% CI: 9.2-20), and 5 (95% CI: 3.6-7.7), respectively. The habitual use of cigarette, alcohol, and betel quids contributed 17% (95% CI: -9, 50%), 61% (95% CI: 25-108%), and 52% more risk of HCC/liver cirrhosis, respectively. The elevated levels of total cholesterol (OR=0.42, 95% CI: 0.33-0.52) and triglyceride (0.57, 95% CI: 0.44-0.74) had inverse association to HCC/liver cirrhosis.

Table 4.8 shows the results of multi-variable logistic regression for HCC/liver cirrhosis. Among all risk factors, low platelet count had the highest adjusted OR (aOR) (5.8, 95% CI: 4.7-7.2). The status of hepatitis virus infection also contributed remarkably for HCC/liver cirrhosis. The aORs for HBV infected only, HCV infected only, and both HBV and HCV infected were 4.6 (95% CI: 3.1-6.8), 5.7 (95% CI: 3.8-8.6), and 5.0 (95% CI: 2.7-9.3). Elevated AFP had almost 4 times risk (95% CI: 2.5-6.3). Elevated GOT had a 3.7-times odds (95% CI: 2.6-5.2). The habitual uses of cigarette, alcohol and betel quids became insignificant. Neither was exercise habit. Nonetheless, the inverse relationship between elevated level of total cholesterol

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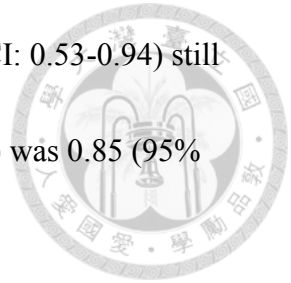
(aOR=0.76, 95% CI: 0.59-0.97) and triglyceride (aOR=0.70, 95% CI: 0.53-0.94) still remained statistically significant. The area under ROC curve (AUC) was 0.85 (95% CI: 0.83-0.87) (Figure 4.2).



4.4 The predictive model with logistic regression for HCC

Table 4.9 shows the estimated results of univariate logistic regression model for HCC with adjustment for age and sex. Male had higher risk for HCC (OR=1.2, 95% CI: 0.76-1.91). Compared to those younger than 55 years old, subjects in the age groups of 55-64 (OR=4.25, 95% CI: 2.36-7.62) and elder than 65 years (OR=2.87, 95% CI: 1.36-6.04) had higher risk of HCC. Among all other risk factors, elevated AFP level (higher than 20 ng/mL) has the highest crude odds ratio (OR) (32, 95% CI: 17-59), followed by the elevated GOT (OR=7.8, 95% CI: 4.9-12.5), low platelet count (OR=7.4, 95% CI: 4.7-11.9), and elevated GPT (OR=4.4, 95% CI: 2.8-7.1). For the hepatitis virus infection, the OR for both HBV and HCV positive, HCV infected only, and HBV infected only was 27 (95% CI: 7-104), 18 (95% CI: 6.2-51), and 8 (95% CI: 3-24), respectively. The habitual use of cigarette, alcohol, and betel quids contributed 52% (95% CI: -20, 187%), 101% (95% CI: 8-277%), and 62% (95% CI: -15, 208%) more risk of HCC, respectively. The elevated levels of total cholesterol (OR=0.31,

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95% CI: 0.17-0.58) and triglyceride (0.46, 95% CI: 0.23-0.92) had inverse association to HCC/liver cirrhosis.

Table 4.10 shows the results of multi-variable logistic regression for HCC. Among all risk factors, hepatitis virus infection was the most remarkable risk factor. The aORs for HBV infected only, HCV infected only, and both HBV and HCV infected were 12.5 (95% CI: 3.2-50), 6.7 (95% CI: 2.2-20), and 7 (95% CI: 2.5-20), respectively. Elevated AFP had almost 6 times risk (95% CI: 3-13). Low platelet count had the aOR of 3.3 (95% CI: 1.9-5.6). Elevated GOT had a 2.5-times odds (95% CI: 1.1-5.6). The AUC was 0.89 (95% CI: 0.85-0.93) (Figure 4.3).

4.5 Survival of HCC

Figure 4.4 shows the survival of HCC patients who were confirmed in our Changhua AUS program. There were 15 HCC deaths among 38 HCC confirmed in the AUS program. The 1-year, 3-year, 5-year, and 8-year survival was 89.2%, 70.7%, 60%, and 56%. The hazard rate given the exponential distribution assumption for survival time was estimated as 0.0951 for the AUS-detected cases. In contrast to the observed survival of HCC in Taiwan where the 1-year and 3-year survival was reported as 58% and 38%, our screen-detected HCC had a better survival. We took the figure of 5-year survival rate of 28.31% for the clinically-detected HCC and transferred it to the hazard rate as 0.2524 given the exponential distribution

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assumption for survival time.

4.6 Evaluation for the effectiveness of AUS for HCC by comparing the empirical HCC mortality with the pseudo control

Based on the proposed pseudo control design, the efficacy of mass AUS screening policy in Changhua was assessed using the comparison between the invited AUS group and the pseudo-control group constructed by using the natural progression from the state of non-cirrhosis, cirrhosis, preclinical state of HCC, and further to HCC death with the consideration of the risk levels evaluated by the risk score constructed by the incorporation of viral hepatitis infection, biomarkers, metabolic factors, and behavior factors.

The observed cumulative mortality for the invited group for AUS along the pseudo-control group with comparable risk level considering the invited group for the first 14 months was first assessed. The results on the cumulative mortality for the comparison was depicted in **Figure 4.5.** During the first year, a total of 12302 subjects was invited to attend the mass AUS screening base on the scheme with the consideration of both the time-frame of the rolling out of the programme and also the risk level of the target population. Among the attendees, 10 HCC death was observed which gives an 81.3 per 100,000 average risk of HCC mortality in fist year. The risk

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of dying from HCC during the first year for the corresponding pseudo-control group was 122.9 per 100,000 in the first year. Based on these estimates, the relative risk of dying from HCC for the invited group compared with the pseudo-pseudo control group was thus 0.66 (95% CI: 0.47-0.92) and the efficacy on HCC mortality reduction was 34% (95% CI: 8-53%). This result is consistent with that reported in previous study based on the principle of intention to treat for the evaluation of service screening programme compared with historical control (age and gender-adjusted relative mortality rate of 0.63 (95% CI: 0.56-0.84).

We further extended the follow-up period to cover the year from the initiation of this mass AUS screening programme of 2008 to the year of 2016 and assessed the effectiveness of this policy based on the same pseudo-control design. The result was depicted in **Figure 4.6**. During the eight-year periods, a total of 122947 person-years was observed in the invited AUS group and 71 subject dying from HCC was observed. Based on the risk-comparable pseudo-control, a total of 183 subject was simulated. The average risk of dying from HCC during eight-year follow-up period for the AUS invited group and the pseudo-control was thus 57.7 and 149.5 per 100,000, respectively. This gives the estimated result on the relative mortality risk of 0.38 (95% CI: 0.32-0.46) and the efficacy of the mass AUS screening policy of 62% mortality reduction for HCC (95% CI: 54-68%).

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4.7 Simulated results of effectiveness of AUS and anti-viral therapy

Table 4.11 shows the simulated results for the pseudo-control group (No screening), the AUS program with empirical coverage rate (the product of invitation rate (Table 4.2) and the attendance rate (Table 4.3)), and the AUS program with 30%, 50%, and 70% compliance to the anti-viral therapy. We applied the simulation to a cohort of 85,147 subjects, the size of current community cohort. Without screening program, there would be 405.8 death from HCC in a 8-year period, with an average mortality rate at 60 per 100,000. When applied the empirical coverage rate from our cohort, the death number reduced to 312.6, which yields the average mortality rate at 46.16 per 100,000. The relative risk (RR) of mortality from HCC compared to no screening was 0.7699 (95% CI: 0.66-0.89). If the AUS was implemented with 30% subjects complying to anti-viral therapy for anti-HBV or anti-HCV positive, the number of HCC death became 223, which results in an average mortality rate of 33 per 100,000. The RR of mortality reduction for AUS plus 30% anti-viral therapy compared to the pseudo-control was 0.5482 (95% CI: 0.47-0.65). When the compliance rate to anti-viral therapy was enhanced to 50% and 70%, the number of HCC death became 190.56, and 170.89, respectively. The corresponding figures for RR were 0.47 (95% CI: 0.39-0.56) and 0.42 (95% CI: 0.35-0.50). The cumulative

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mortality curve with pseudo-control, AUS, AUS plus anti-viral therapy with compliance rate of 30%, 50%, and 70% was shown in Figure 4.7.

We also examined the enhancement of coverage rate for those in the intermediate risk group. When AUS combined with 30% anti-viral therapy, the enhancement of coverage rate to 75% for those in the intermediate group resulted in 212.3 HCC deaths, which yield RR as 0.5226 (95% CI: 0.44-0.62).

4.8 Cost-effectiveness analysis for the Changhua AUS Screening

Table 4.12 shows the results of cost-effectiveness analysis for the Changhua AUS screening program. Given a cohort with 85,147 subjects, our Changhua AUS program required $6.22 million more incurred in cost in order to gain 272 person years, which lead to an incremental cost-effectiveness ratio (ICER) at 22849.34. Combined AUS and anti-viral therapy of compliance rate at 30%, the ICER increased to 101.849. The compliance rate at 50% in adjunction with AUS brought up the ICER to 141,805. A further enhancement of compliance to anti-viral therapy to 70% would result in a higher ICER at 181,919. Interestingly, the ICER for the program with an increase attendance rate for AUS in the intermediate group combined with 30% anti-viral therapy had an ICER at 102,306, which was slightly higher than its counterpart with empirical coverage rate program (101,849). The cost-effectiveness plane was

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shown in Figure 4.8.

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Table 4.1 The distribution of age and risk groups for eligible in the Ultrasound screening, Changhua

Age Group	Group A				Group B				Total
	EH		H		IM		L		
45-49	914	6.51%	1669	11.89%	930	6.63%	10524	74.97%	14037
50-54	1763	9.30%	1793	9.45%	1730	9.12%	13680	72.13%	18966
55-59	1864	9.37%	1714	8.62%	3641	18.31%	12669	63.70%	19888
60-64	1750	10.08%	1188	6.84%	6898	39.73%	7527	43.35%	17363
65-69	1897	14.44%	413	3.14%	5886	44.81%	4939	37.60%	13135
70-74	242	13.77%	39	2.22%	906	51.54%	571	32.48%	1758
Total	8430	9.90%	6816	8.00%	19991	23.48%	49910	58.62%	85147

Table 4.2 The distribution of age and risk groups for invitation in the Ultrasound screening, Changhua

Age Groups	Invitation					Invitation Rate				
	Group A		Group B		Total	Group A		Group B		Total
	EH	H	IM	L		EH	H	IM	L	
45-49	860	1554	191	155	2760	94.09%	93.11%	20.54%	1.47%	19.66%
50-54	1669	1735	332	304	4040	94.67%	96.77%	19.19%	2.22%	21.30%
55-59	1778	1674	694	444	4590	95.39%	97.67%	19.06%	3.50%	23.08%
60-64	1695	1149	1483	146	4473	96.86%	96.72%	21.50%	1.94%	25.76%
65-69	1868	399	2118	141	4526	98.47%	96.61%	35.98%	2.85%	34.46%
70-74	241	38	203	21	503	99.59%	97.44%	22.41%	3.68%	28.61%
Total	8111	6549	5021	1211	20892	96.22%	96.08%	25.12%	2.43%	24.54%

Table 4.3 The distribution of age and risk groups for attendance in the Ultrasound screening, Changhua

Age Groups	Subjects					Attendance Rate				
	Group A		Group B		Total	Group A		Group B		Total
	EH	H	IM	L		EH	H	IM	L	
45-49	651	1141	115	97	2004	75.70%	73.42%	60.21%	62.58%	72.61%
50-54	1278	1330	234	183	3025	76.57%	76.66%	70.48%	60.20%	74.88%
55-59	1404	1307	510	281	3502	78.97%	78.08%	73.49%	63.29%	76.30%
60-64	1356	905	1090	105	3456	80.00%	78.76%	73.50%	71.92%	77.26%
65-69	1532	319	1621	79	3551	82.01%	79.95%	76.53%	56.03%	78.46%
70-74	201	32	169	17	419	83.40%	84.21%	83.25%	80.95%	83.30%
Total	6422	5034	3739	762	15957	79.18%	76.87%	74.47%	62.92%	76.38%

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Table 4.4 The clinical diagnosis of ultrasound and confirmed HCC by risk groups

Ultrasonography Findings and Confirmatory Diagnosis	Group A				Group B				Total	
	E-H		H		IM		L			
	No.	DR*	No.	DR	No.	DR	No.	DR	No.	DR
Total screens	15521		11860		7388		1185		35954	
Confirmatory HCC	65	4.19	4	0.34	4	0.54	0	0.00	73	2.03
Liver cirrhosis	888	57.21	70	5.90	100	13.54	3	2.53	1061	29.51
Liver nodule	688	44.33	257	21.67	143	19.36	23	19.41	1111	30.90
Liver hemangioma	766	49.35	648	54.64	320	43.31	28	23.63	1762	49.01
Liver parenchymal disease	4145	267.06	2266	191.06	784	106.12	78	65.82	7273	202.29

*DR: Detection rate per 1,000.

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Table 4.5 Distribution of ultrasound findings by age, sex and risk group at prevalent screen

	N	LC	Prevalence rate (per 1000)	HCC	Prevalence rate (per 1000)
Total	16187	255	15.8	38	2.3
Risk group					
EH	6535	214	32.7	34	5.2
H	5125	24	4.7	3	0.6
IM	3759	15	4.0	1	0.3
L	768	2	2.6	0	0.0
Male					
45-49	986	14	14.2	2	2.0
50-54	1416	37	26.1	1	0.7
55-59	1635	32	19.6	8	4.9
60-64	1606	31	19.3	6	3.7
65-69	1622	16	9.9	4	2.5
70-79	342	5	14.6	0	0.0
Subtotal	7607	135	17.7	21	2.8
Female					
45-49	1396	9	6.4	2	1.4
50-54	1875	18	9.6	3	1.6
55-59	1947	28	14.4	1	0.5
60-64	1644	33	20.1	4	2.4
65-69	1470	27	18.4	5	3.4
70-79	244	3	12.3	0	0.0
Subtotal	8576	118	13.8	15	1.7

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Table 4.6 Incidence of liver cirrhosis and HCC since previous negative screening findings

	PY	LC	Incidence rate (per 100,000)	PY	HCC	Incidence rate (per 100,000)
Total	30524	150	491.41	31585	39	123.47
Risk group						
EH	12031	126	1047.27	12888	35	271.57
H	10245	13	126.89	10350	1	9.66
IM	7454	10	134.15	7542	3	39.78
L	794	1	125.96	805	0	0.00
Male						
45-49	414	1	241.68	418	0	0.00
50-54	1642	13	791.76	1690	0	0.00
55-59	2451	12	489.62	2583	4	154.88
60-64	2864	21	733.16	2985	4	133.99
65-69	2956	15	507.53	3074	7	227.73
70-79	3249	23	707.82	3335	3	89.97
Subtotal	13576	85	626.12	14084	18	127.81
Female						
45-49	747	1	133.90	754	0	0.00
50-54	2653	7	263.84	2703	1	37.00
55-59	3669	15	408.82	3741	1	26.73
60-64	4043	26	643.08	4205	6	142.68
65-69	3302	8	242.30	3451	5	144.88
70-79	2535	8	315.59	2648	8	302.12
Subtotal	16949	65	383.51	17502	21	119.99

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Table 4.7 Univariate analysis for the risk of liver cirrhosis or HCC adjusting for age and sex with logistic regression model

Variables	OR	95% CI	
Age group			
35-54	1.00		
55-64	1.53	1.25	1.88
65+	1.31	0.99	1.72
Sex (Male vs Female)	1.37	1.14	1.65
Cigarette Smoking	1.17	0.91	1.50
Alcohol Drinking	1.61	1.25	2.08
Betel Quids Chewing	1.52	1.18	1.97
Exercise	0.94	0.78	1.14
Type 2 diabetes	1.05	0.83	1.34
Total cholesterol(≧200 vs <200 mg/dl)	0.42	0.33	0.52
Triglyceride(≧150 vs <150 mg/dl)	0.57	0.44	0.74
GOT(≧45 vs <45 IU/L)	7.72	6.36	9.36
GPT(≧45 vs <45 IU/L)	4.12	3.40	4.99
Platelet count(<150 vs ≧ 150X10^3)	9.72	8.02	11.78
Hepatitis			
HBV(-) HCV(-)	1.00		
HBV(+) HCV(-)	5.24	3.59	7.66
HBV(-) HCV(+)	13.55	9.25	19.84
HBV(+) HCV(+)	11.69	6.53	20.93
AFP (≧20 vs <20 ng/mL)	22.79	15.56	33.37

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Table 4.8 Multi-variable logistic regression for confirmed HCC or liver cirrhosis

Variables	aOR	95% CI	
Age group			
35-54	1.00		
55-64	1.51	1.20	1.89
65+	1.43	1.04	1.95
Sex (Male vs Female)	1.59	1.22	2.07
Cigarette Smoking	0.88	0.64	1.21
Alcohol Drinking	1.29	0.95	1.76
Betel Quids Chewing	1.28	0.92	1.79
Exercise	0.97	0.79	1.19
Type 2 diabetes	1.32	1.02	1.73
Total cholesterol(≧200 vs <200 mg/dl)	0.76	0.59	0.97
Triglyceride(≧150 vs <150 mg/dl)	0.70	0.53	0.94
GOT(≧45 vs <45 IU/L)	3.66	2.58	5.20
GPT(≧45 vs <45 IU/L)	1.04	0.74	1.46
Platelet count(<150 vs ≧150X10^3)	5.80	4.69	7.17
AFP (≧20 vs <20 ng/mL)	3.95	2.47	6.30
Hepatitis			
HBV(-) HCV(-)	1.00		
HBV(+) HCV(-)	4.59	3.13	6.75
HBV(-) HCV(+)	5.73	3.83	8.57
HBV(+) HCV(+)	5.00	2.69	9.32

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Table 4.9 Univariate analysis for the risk of HCC adjusting for age and sex with logistic regression model

Variables	OR	95% CI	
Age group			
35-54	1.00		
55-64	4.25	2.36	7.62
65+	2.87	1.36	6.04
Sex (Male vs Female)	1.21	0.76	1.91
Cigarette Smoking	1.52	0.80	2.87
Alcohol Drinking	2.01	1.08	3.77
Betel Quids Chewing	1.62	0.85	3.08
Exercise	0.85	0.54	1.35
Type 2 diabetes	1.15	0.66	1.90
Total cholesterol(≧200 vs <200 mg/dl)	0.31	0.17	0.58
Triglyceride(≧150 vs <150 mg/dl)	0.46	0.23	0.92
GOT(≧45 vs <45 IU/L)	7.84	4.93	12.47
GPT(≧45 vs <45 IU/L)	4.44	2.79	7.06
Platelet count(<150 vs ≧ 150X10^3)	7.44	4.67	11.86
Hepatitis			
HBV(-) HCV(-)	1.00		
HBV(+) HCV(-)	8.35	2.91	23.94
HBV(-) HCV(+)	17.83	6.19	51.40
HBV(+) HCV(+)	27.36	7.23	103.57
AFP (≧20 vs <20 ng/mL)	31.86	17.10	59.34

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Table 4.10 Multi-variable logistic regression for confirmed HCC

Variables	aOR		95% CI
Age group			
35-54	1.00		
55-64	4.3	2.34	7.914
65+	3.37	1.54	7.347
Sex (Male vs Female)	1.3	0.68	2.476
Cigarette Smoking	1.07	0.5	2.285
Alcohol Drinking	1.62	0.8	3.307
Betel Quids Chewing	1.12	0.52	2.394
Exercise	0.91	0.56	1.476
Type 2 diabetes	1.64	0.92	2.91
Total cholesterol(≧200 vs <200 mg/dl)	0.61	0.31	1.165
Triglyceride(≧150 vs <150 mg/dl)	0.57	0.27	1.204
GOT(≧45 vs <45 IU/L)	2.47	1.09	5.573
GPT(≧45 vs <45 IU/L)	1.34	0.62	2.885
Platelet count(<150 vs ≧150X10^3)	3.3	1.94	5.617
AFP (≧20 vs <20 ng/mL)	6.28	2.98	13.24
Hepatitis			
HBV(-) HCV(-)	1.00		
HBV(+) HCV(-)	7.08	2.45	20.47
HBV(-) HCV(+)	6.67	2.22	20.09
HBV(+) HCV(+)	12.5	3.17	49.55

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Table 4.11 Estimated effectiveness of abdominal ultrasonography screening on the basis of 85,147 subjects

Strategy	Death of HCC	Cumulative person-years	Mort (per 10^5)	RR
No screening	405.81	676,771	59.96	
Risk-based AUS screening	312.57	677,096	46.16	0.7699 (0.66-0.89)
Risk-based AUS screening with 30% anti-virus therapy	222.66	677,393	32.87	0.5482 (0.47-0.65)
Risk-based AUS screening with 50% anti-virus therapy	190.56	677,499	28.13	0.4691 (0.39-0.56)
Risk-based AUS screening with 70% anti-virus therapy	170.89	677,564	25.22	0.4206 (0.35-0.50)
Risk-based AUS screening with 30% anti-virus therapy and enhanced attendance for IM	212.27	677,431	31.33	0.5226 (0.44-0.62)

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Table 4.12 Simulated results for the cost-effectiveness analysis for screening strategies to prevent HCC on the basis of 85,147 subjects

Strategy	Cost ($)	Incremental cost	Effectiveness	Incremental Effectiveness	ICER
No screening	19,696,960		593,987		
Risk-based AUS screening	25,916,892	6,219,933	594,259	272	22,849.34
Risk-based AUS screening with 30% anti-virus therapy	72,770,528	53,073,569	594,508	521	101,849.18
Risk-based AUS screening with 50% anti-virus therapy	106,161,083	86,464,124	594,596	610	141,805.45
Risk-based AUS screening with 70% anti-virus therapy	140,470,657	120,773,697	594,651	664	181,918.92
Risk-based AUS screening with 30% anti-virus therapy and enhanced attendance for IM	76,266,512	56,569,553	594,540	553	102,306.00

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Figure 4.1 The flow chart of abdominal ultrasound screening, Changhua, 2005-2017

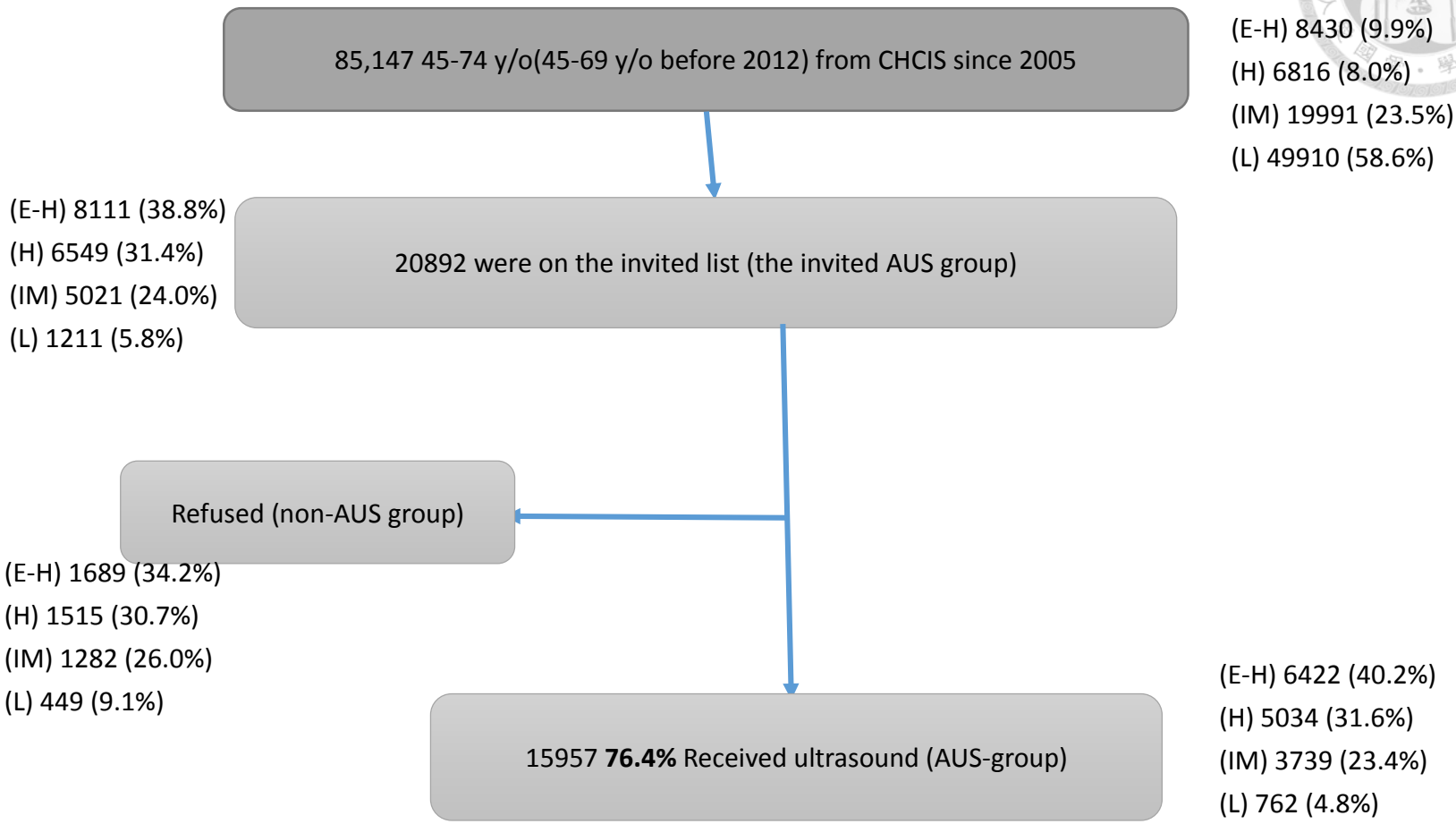

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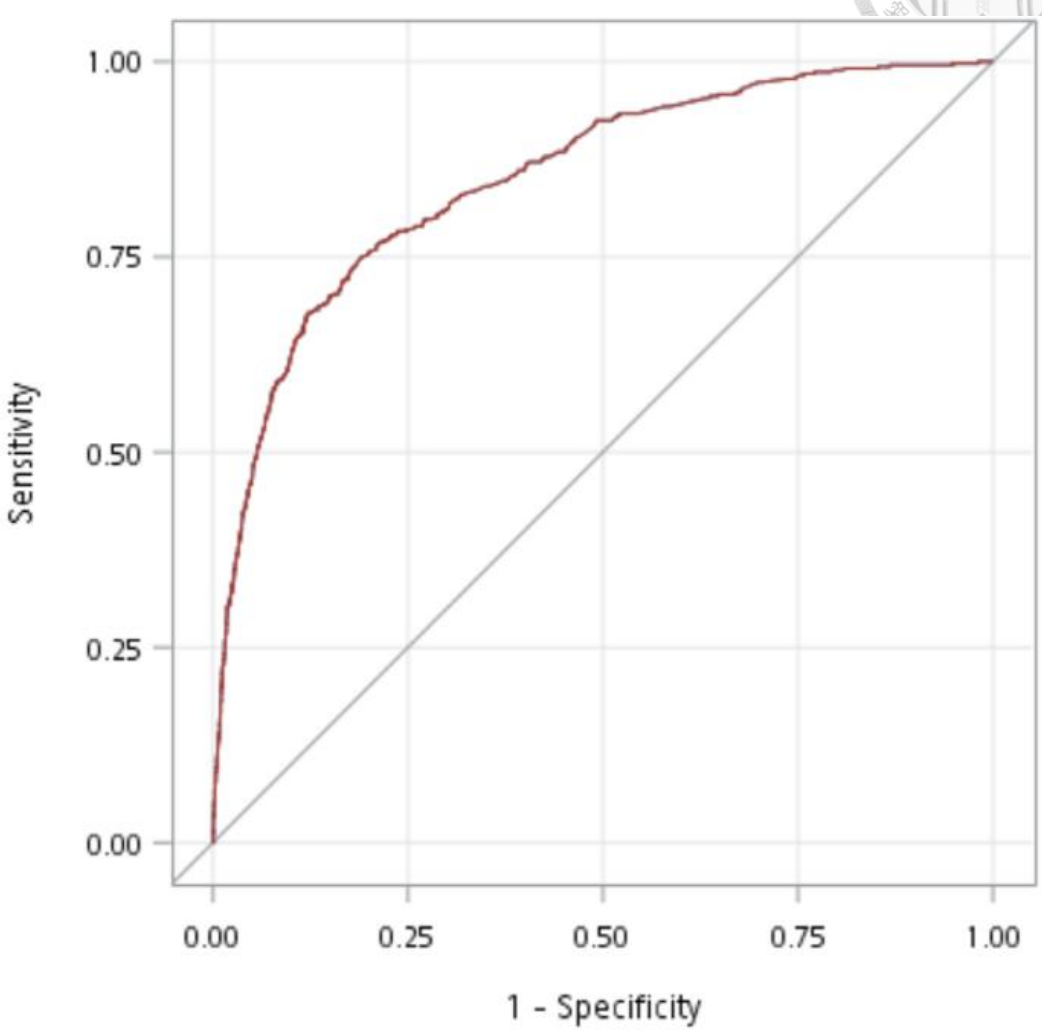
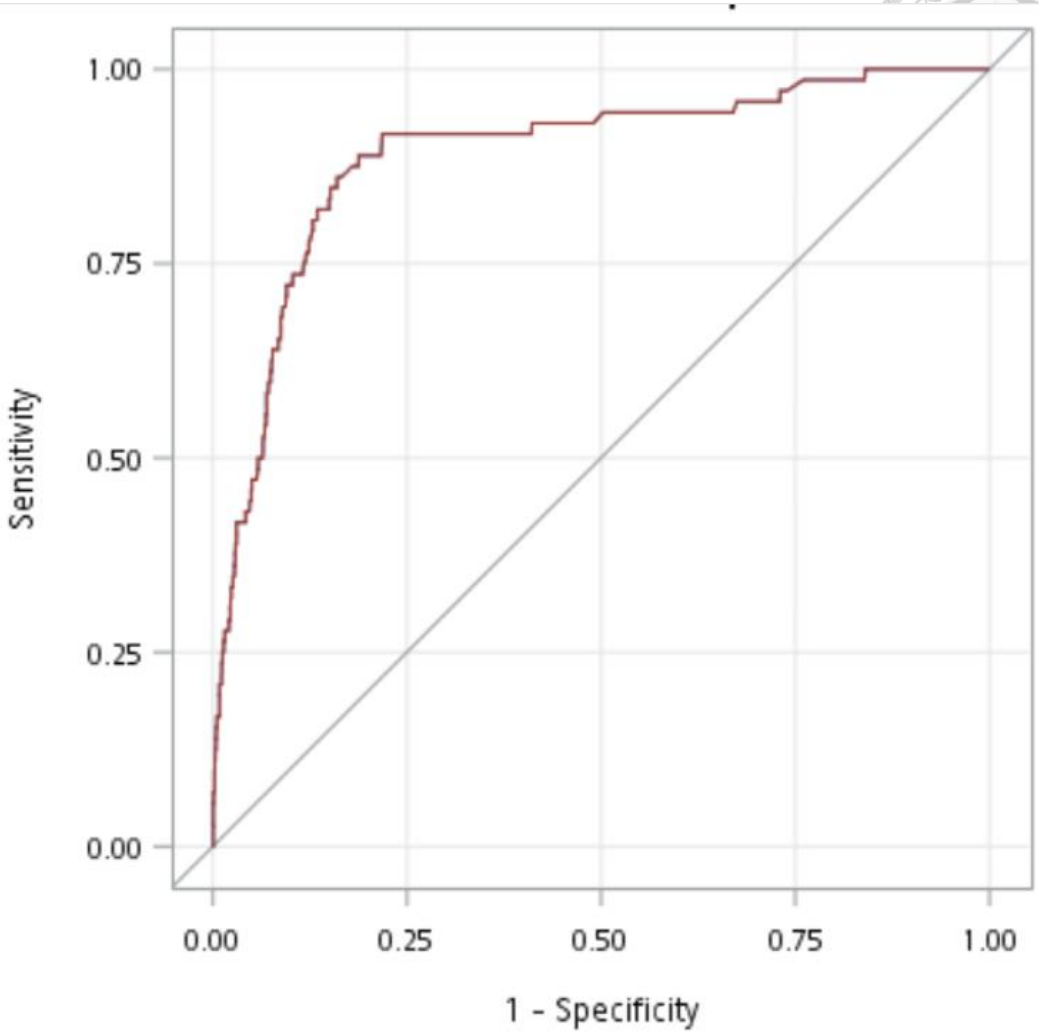
Figure 4.2 The ROC curve for multi-variable logistic regression for confirmed HCC or liver cirrhosis



AUROC 0.85, 95% CI (0.83,0.87)

doi:10.6342/NTU201802411

Figure 4.3 The ROC curve for multi-variable logistic regression for confirmed HCC



AUROC 0.89, 95% CI (0.85,0.93)

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Figure 4.4 The HCC cases survival rate for Taiwan and Changhua AUS detected cases

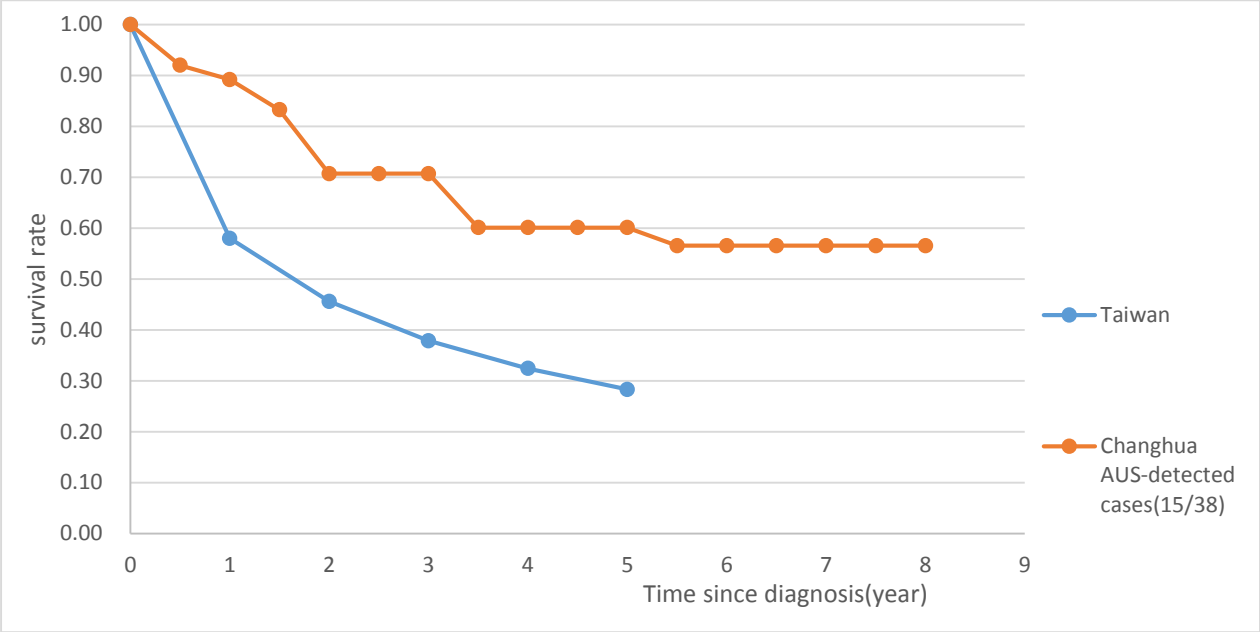

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Figure 4.5 Cumulative HCC mortality for the invited AUS group and the corresponding pseudo-control group for first 14 months

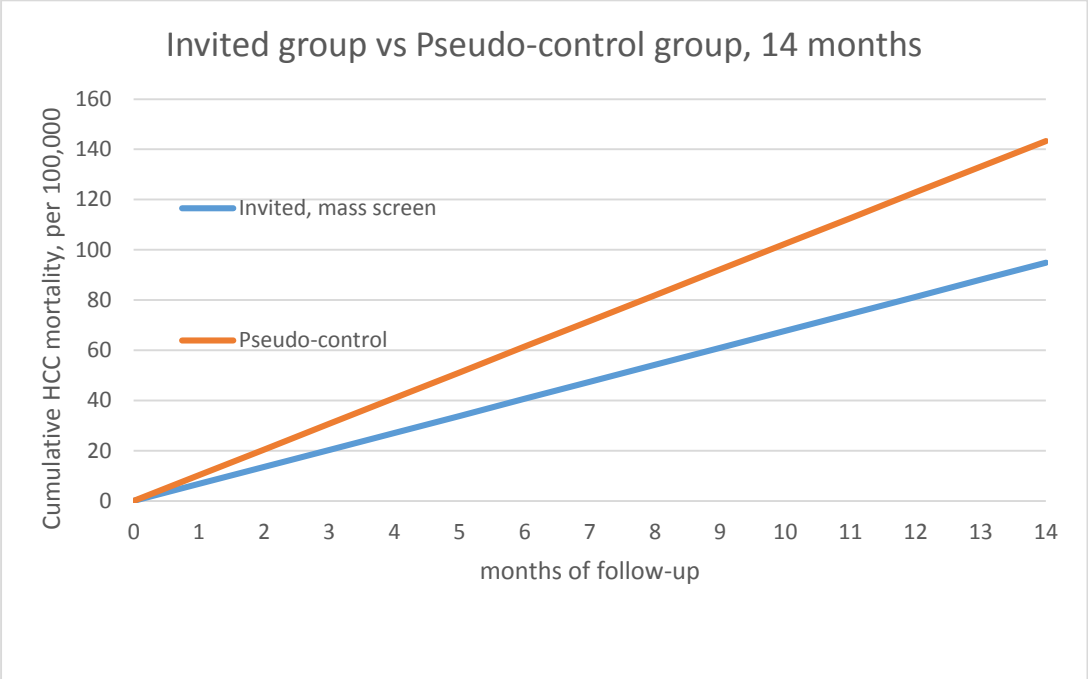

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Figure 4.6 Cumulative HCC mortality for the invited AUS group and the corresponding pseudo-control group for 8 years

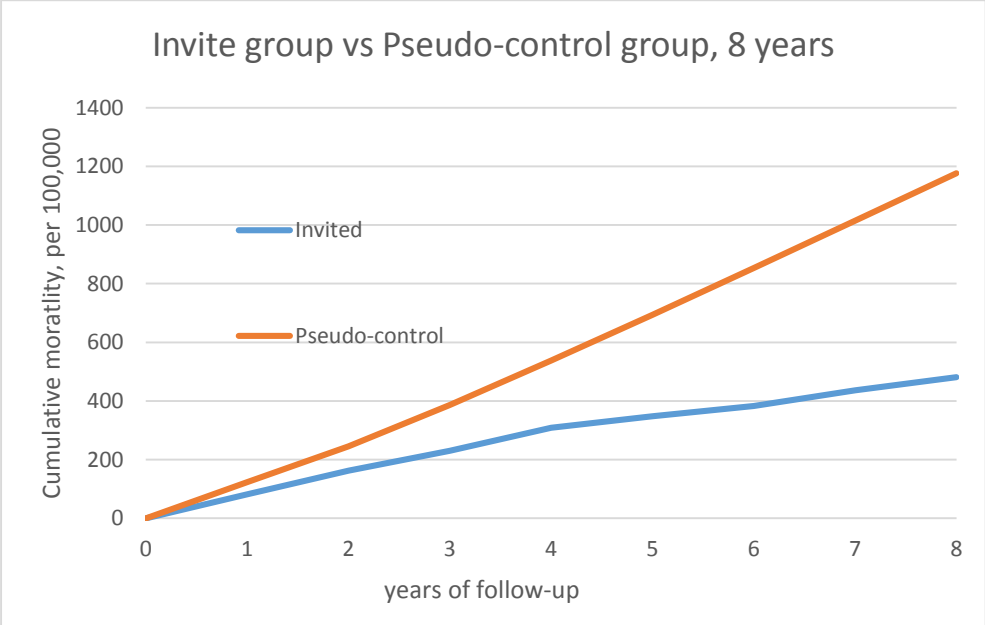

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Figure 4.7 The cumulative mortality for HCC with difference AUS and anti-viral therapy strategies

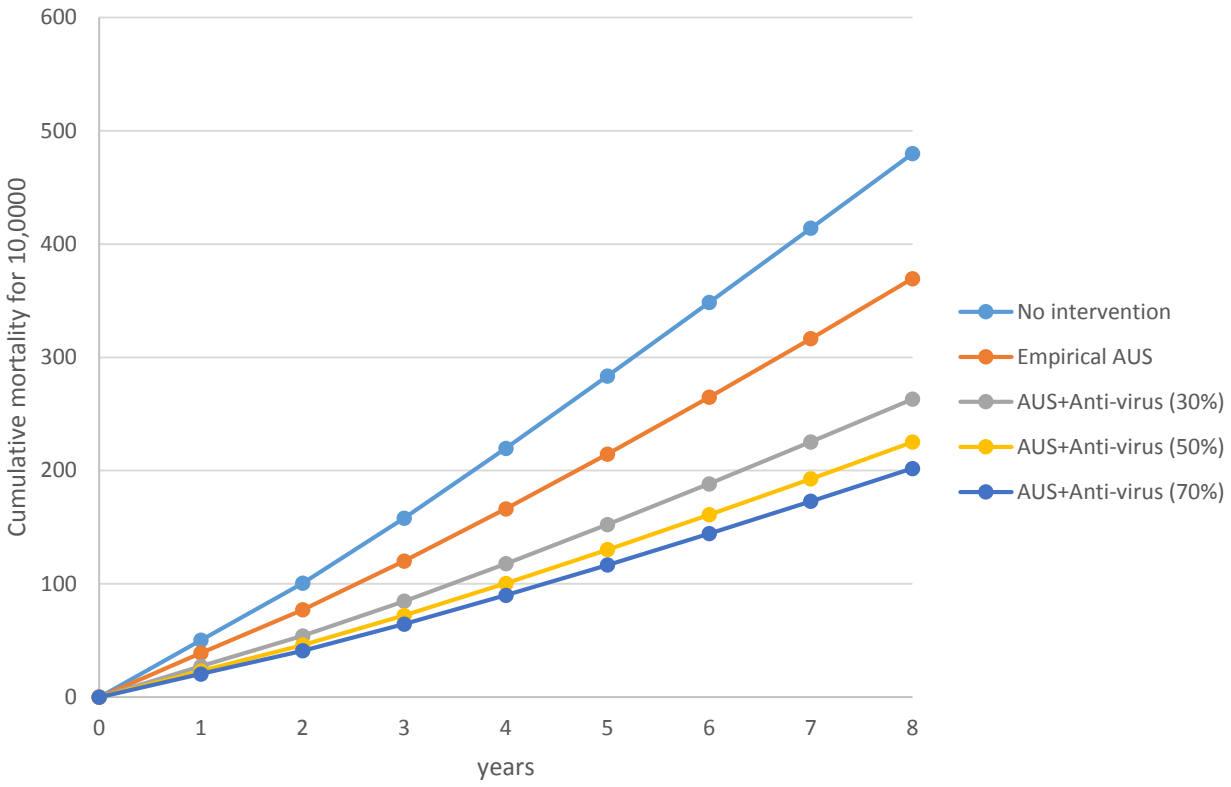

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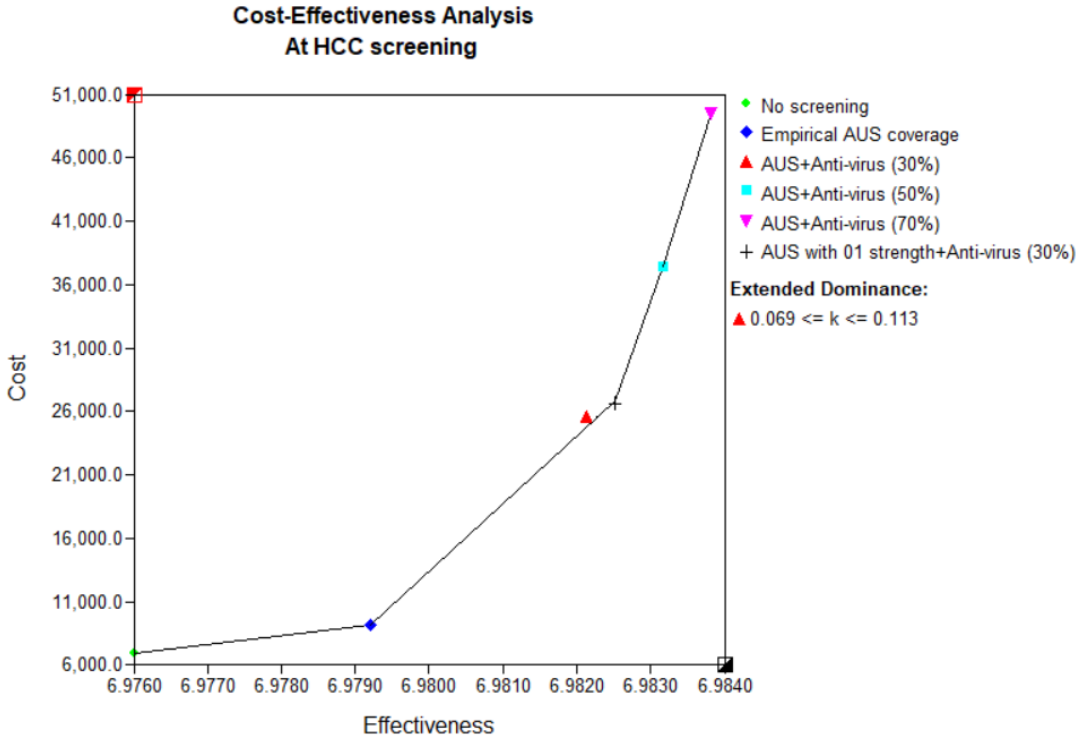
Figure 4.8 The cost-effectiveness plane for the Changhua AUS Screening combined with ant-viral therapy



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Chapter 5 Discussion

5.1 Summary of main findings

There are several major findings noted in this thesis. The empirical findings on effectiveness and cost-effectiveness include

(1) The predictive validity of the risk prediction model for HCC is very good on the basis of ROC curve performance with AUC higher up to 0.89 (95% CI: 0.85-0.93);

(2) The observed 8-year HCC mortality reduction with AUS by risk groups together with around 30% coverage rate of anti-viral therapy was around 66% (RR=0.39, 95% CI: 0.32-0.46);

(3) The simulated results by using the pseudo-control group indicate additional contribution of 30% compliance rate of anti-viral therapy (empirical estimate) to HCC mortality reduction was around 22%. The corresponding figures are raised to 30% and 35% when the compliance rate of anti-viral therapy is enhanced to 50% and 70%, respectively.

(4) The simulated results by using the pseudo-control group show 3% HCC mortality reduction attributable to additional contribution of screening intermediate risk group with AUS when the coverage rate of this group is enhanced from 25% to 75%.;

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(5) The results of health economic decision model show the ICER (incremental cost-effectiveness ratio) values were $22,849 for the administration of AUS, $101,849 for the administration of AUS plus 30% compliance to anti-viral therapy. The corresponding figure for 50% and 70% compliance rate to anti-viral therapy were $141,805 and $181,919, respectively.

The methodological aspect of this thesis include

(1) the development of the pseudo-control group by building up the disease natural history of progression of HCC embedded with the risk prediction model for HCC and the survival of HCC by detection modes;

(2) the use of the pseudo-control model provides an opportunity

(3) the development of health economic decision model for cost-effectiveness of various preventive strategies.

5.2 Predictive model for HCC

Our study developed predictive models of binary outcome and multi-state process for developing HCC based on a community-based longitudinal follow-up cohort after the administration of abdominal ultrasonography. The application of the predictive model to generating risk score for each individual from the underlying population has

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a significant implication for mass screening for HCC with abdominal ultrasonography targeted at general population. Although there are a variety of preventive strategies for preventing death from HCC such as routine ultrasonography checkup or surveillance of AFP, the majorities are limited to high-risk subjects with HBV or HCV infected. For the derivation of the risk score used in our population-based AUS screening in terms of effective and efficient purpose, we require information on demographic characteristics of age and sex, and the behavior risk factors including smoking status, status of alcohol consumption, and status of betel-nut chewing, exercise habit, the comorbidity of diabetes, laboratory examination including total cholesterol level, triglycerol level, GOT, GPT and platelet count. Such information is often readily available in routine health check-up for adults. Based on information specified above, out risk scoring system for HCC reached the accuracy of 89% (95% CI: 85-93%) Taking into account both HCC and liver cirrhosis, the accuracy of our risk stratification tool was estimated as 85% (95% CI: 83-87%). These results show the aspect of validity of our risk stratification tool. Given the consideration in medical capacity of using AUS as a screening tool, the developed tool in risk stratification provides a solution toward effective and efficient population-based approach with the consideration of individualize risk levels in terms of liver cirrhosis and HCC.

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Considering the multistate nature in the development of HCC, it is crucial to evaluate the effect of risk factors on the process of HCC evolution. In general, male had a higher risk of the development of liver cirrhosis, preclinical HCC, and HCC compared with female population. Our results confirmed the observation in previous study that while HBV infection carries an elevated risk for HCC progression subjects, HCV infection and also the co-infection of HBV and HCV had a soaring risk with the aHR estimated as high as 15-fold compared with viral hepatitis naïve subject.

5.3 The disease natural history of HCC

To create the pseudo-control group, in addition to the development of predictive model, the formulation of disease natural history model is very important. We further elucidate the effect of viral hepatitis on the mechanism of HCC progression by using four-state Markov model. Based on our four-state progressive model of HCC evolution, the effect of viral infection predominantly exerts their effect on the development of liver cirrhosis, although the co-infection of HBV and HCV may also have effect on the progression from liver cirrhosis to preclinical (asymptomatic) HCC with the aHR estimated as 2.07 (95% CI: 0.92-2.32). Although the main effect of the status viral infection on the progression of HCC have been considered in our four-state Markov regression model, the difference between male and female in terms of

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the development of liver cirrhosis, the progression from liver cirrhosis to preclinical HCC and also the development from preclinical HCC to clinical HCC. This may be due to other factors such as bahaviour factors (alcohol consumption and betel-nut chewing) and comorbid status (diabetes and metabolic syndrome) that carries differently by male and female subject. This can be elucidated on the basis of the framework of proposed four-state progressive model of HCC with the incorporation of relevant factors a covariate in the Markov regression model.

5.4 The value of pseudo-control group

The importance on the evaluation of population-based screening programme can never be overemphasized. However, evaluating of population-based service screening by risk group as seen in the current AUS program, the selection of the comparator is always difficult. By using the proposed four-state Markov model, the natural progression can be constructed on the basis of the estimated results which constitute the pseudo-control group for the evaluation of screening efficacy. Furthermore, the estimation for the parameters governing the progression of HCC is based on the empirical data of the population invited to attend the screening programme. This provides a sound ground for the comparability between the intervention group that is

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derived from the observed data of the AUS screening programme and the comparator that is derived from the projection using the natural progression model.

The most important value of using the pseudo-control group is that is enables us to estimate each independent contribution of AUS and anti-viral therapy to HCC mortality reduction. In addition, the simulated results by various compliance rates in relation to anti-viral therapy and coverage rates by risk groups were implemented by the application of pseudo-control group as did in this thesis.

5.5 Limitations

There are two main limitations of this thesis. First, the risk prediction model has included the risk prediction for cirrhosis but the effectiveness of AUS has not considered the possible reduction of mortality from cirrhosis. This may account for why there is only 3% extra mortality reduction when 25% coverage rate of the intermediate risk group was increased to 75%. Second, cost-effectiveness analysis was based on deterministic mode rather than probabilistic one that precludes one from producing the simulated results of C-E plane and acceptability curve.

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Chapter 6 Conclusion

The population-based screening programme for HCC in Changhua confirmed the validity and feasibility for the developed risk score applied in our screening programme. We further used a computer study design with a pseudo-control group that was developed on the basis of disease natural history of HCC embedded with the predictive model and the survival part of HCC to estimate long-term effectiveness of the overall and marginal effectiveness and cost-effectiveness of AUS and anti-viral therapy.

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