國立台灣大學公共衛生學院流行病學與預防醫學研究所

博士論文

Graduate Institute of Epidemiology and Preventive Medicine,
College of Public Health, National Taiwan University

Doctoral Dissertation

抗 B 型肝炎病毒藥物治療之長期療效評估

Long-Term Effectiveness of Antiviral Therapy for Patients with Chronic Hepatitis B

葉怡君

Yi-Chun Yeh

指導教授：賴美淑 教授

Advisor: Mei-Shu Lai, MD, PhD

中華民國 104 年 6 月

June, 2015

國立臺灣大學博士學位論文
口試委員會審定書

抗 B 型肝炎病毒藥物治療之長期療效評估

Long-Term Effectiveness of Antiviral Therapy for Patients with Chronic Hepatitis B

本論文係 葉怡君 君（學號 D00849007）在國立臺灣大學流行病學與預防醫學研究所完成之博士學位論文，於民國 104 年 6 月 17 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：

賴美淑 （簽名）

（指導教授）

陳培哲　　李文宗

邱文達　　劉俊人

陳建仁　　杜裕康

摘要

研究背景與目的：

B 型肝炎是常見的傳染性疾病，許多末期肝病(如：肝硬化、肝癌)的發生與肝癌復發，皆與 B 型肝炎感染有關。因此，B 型肝炎防治計畫，除了藉由疫苗防治控制 B 型肝炎感染外，必須透過更積極抗病毒藥品治療，控制 B 型肝炎病毒，舒緩肝臟發炎狀況，以期望延緩或降低肝硬化與肝癌的發生與復發。雖然過去研究業已指出抗病毒藥品降低肝硬化與肝癌發生與復發的療效，然而受限於研究樣本數，結果未有一致性。因此，本研究將評估 (1) 慢性 B 型肝炎病人，接受有治療期限規定之 lamivudine、interferon 或 peg-interferon 治療的長期療效，以及 (2) B 型肝炎相關肝癌且接受治癒性肝癌治療病患，後續接受輔助性抗病毒治療的長期療效。

研究材料與方法：

本研究利用全民健康保險資料庫(National Health Insurance, NHI)與癌症登記資料庫(Taiwan Cancer Registry, TCR)建立世代研究，選取研究 2004 至 2010 年間，診斷為慢性 B 型肝炎病人，與新診斷並接受治癒性肝癌治療之 B 型肝炎相關肝癌病人，為研究對象。利用治療機率倒數加權(Inverse probability of treatment weighting, IPTW)以及傾向分數配對(Propensity score matching)進行校正，以 Cox 比例風險模式(Cox proportional hazard model)，估計研究事件之風險比(Hazard ratios, HRs)與 95%信賴區間(confidence intervals, CIs)。

研究結果：

於慢性 B 型肝炎病患研究中，相較於未治療組，有治療期限規定下 lamivudine 能有效降低肝癌 (HR, 0.46; 95%CI, 0.41-0.51)、肝臟相關疾病死亡(HR,0.68; 95%CI, 0.61-0.77)，以及全死因死亡(HR, 0.70; 95%CI, 0.64-0.76)的發生。此療效於有治療期限規定之 interferon 治療亦可發現相似的結果(肝癌：HR, 0.22; 95%CI, 0.15-0.31；肝臟相關疾病死亡：HR, 0.14; 95%CI, 0.07-0.27；全死因死亡：HR, 0.10; 95%CI, 0.06-0.18)。

於 B 型肝炎相關肝癌且接受治癒性肝癌治療病患研究中，接受輔助性抗病毒治療的病患，相較於未治療組，有較高風險的肝癌復發 (HR, 1.19; 95%CI, 1.03-1.37)，以及全死因死亡(HR, 1.22; 95%CI, 0.98-1.51)的發生。於治癒性肝癌治療後，不同時間點接受輔助性抗病毒治療，與肝癌復發及全死因死亡發生無顯著性相關。

結論：

本研究證實有治療期限規定之 lamivudine, interferon 與 peg-interferon 抗 B 型肝炎病毒藥品，用於治療慢性 B 型肝炎病患，可有效降低肝癌與死亡發生。然而，將抗 B 型肝炎病毒藥品，用於輔助治療 B 型肝炎相關肝癌且接受治癒性肝癌治療病患，則未觀察到其降低肝癌復發與死亡發生之療效。

關鍵字：慢性 B 型肝炎、B 型肝炎相關肝癌、抗病毒治療、肝癌、死亡

ABSTRACT

BACKGROUND AND OBJECTIVE:

Hepatitis B virus (HBV) is one of high prevalence and serious global health problem. The end-stage liver diseases incidence and hepatocellular carcinoma (HCC) incidence or recurrence may be attributed to viral hepatitis B. Therefore, HBV control programs must be augmented by active antiviral treatment among patients with chronic hepatitis B (CHB) or HBV-related HCC. The efficacy of anti-HBV treatments in mitigating the incidence or recurrence of HCC and mortality has not yet been substantiated. This study was (1) to evaluate the effects of finite-period lamivudine (LAM) and interferon (IFN) or peg-interferon (PEG-IFN) treatments on HCC development and mortality among CHB patients, as well as (2) to investigate the effect of adjuvant antiviral therapies on HCC progression and deaths in HBV-related HCC patients following curative treatment.

MATERIALS AND METHODS:

A nationwide inception cohorts of CHB patients and newly diagnosed HBV-related HCC patients who received curative HCC therapy as the first course of treatment for the years 2004 to 2010 were identified from the National Health Insurance (NHI) program and the Taiwan Cancer Registry (TCR), respectively. This study employed a Cox proportional hazards model based on inverse probability of treatment weighting (IPTW) and propensity score matching to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

RESULTS:

CHB patients who underwent finite-period lamivudine treatment presented greater reductions in HCC incidence (HR, 0.46; 95%CI, 0.41-0.51), liver-related mortality (HR, 0.68; 95%CI, 0.61-0.77), and all-cause mortality (HR, 0.70; 95%CI, 0.64-0.76) than patients in the untreated group. Finite-period interferon or peg-interferon therapy resulted in similar reductions in HCC incidence (HR, 0.22; 95%CI, 0.15-0.31), liver-related mortality (HR, 0.14; 95%CI, 0.07-0.27), and all-cause mortality (HR, 0.10; 95%CI, 0.06-0.18).

HBV-related HCC patients following curative therapy who underwent adjuvant antiviral therapy demonstrated a higher risk of HCC progression (HR, 1.19; 95%CI, 1.03-1.37) and death from all causes (HR, 1.22; 95%CI, 0.98-1.51) than untreated patients. The interval length between initiation of antiviral therapy and first-line curative treatment did not show a significant association with HCC progression and all-cause mortality.

CONCLUSIONS:

Our results demonstrate the effectiveness of finite-period lamivudine, interferon, or peg-interferon anti-HBV therapy in reducing the incidence of HCC and mortality in the long-term follow-up of a large CHB patient population. However, this effect did not be found in reducing the risk of HCC progression or mortality in HBV-related HCC patients after curative therapy.

KEY WORDS: Chronic hepatitis B, Hepatitis B Virus-related Hepatocellular carcinoma, Antiviral therapy, Hepatocellular carcinoma, Mortality

CONTENTS

摘要 I

ABSTRACT III

CONTENTS V

CONTENTS OF TABLES VII

CONTENTS OF FIGURES IX

CHAPTER 1 BACKGROUND 1

CHAPTER 2 LITERATURE REVIEW 3

2.1 Natural history of chronic hepatitis B 3

2.2 Antiviral therapies to prevent occurrence of hepatocellular carcinoma 6

2.2.1 Evolution of anti-HBV therapies 6

2.2.2 Specific intervention 8

2.2.3 Reimbursement under the Taiwan National Health Insurance program for antiviral therapy for hepatitis B virus 11

2.3 Adjuvant antiviral therapy to prevent recurrence of hepatocellular carcinoma 12

2.4 Biases in retrospective cohort studies based on secondary databases 14

2.5 Summary 18

CHAPTER 3 STUDY AIM AND FRAMEWORK 20

3.1 Study aim 20

3.2 Study framework 20

CHAPTER 4 MATERIALS AND METHODS 22

4.1 Effectiveness research of lamivudine or interferon/peginterferon in chronic hepatitis B patients 22

4.2 Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment 28

CHAPTER 5 RESULTS 35

5.1 Effectiveness research of lamivudine or interferon/peginterferon in Chronic Hepatitis B patients 35

5.2 Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment 59

CHAPTER 6 DISCUSSIONS 71

6.1 Effectiveness research of lamivudine or interferon/peginterferon in Chronic Hepatitis B patients 71

6.2 Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment 75

6.3 Strengths and limitations 82

CHAPTER 7 CONCLUSION 86

REFERENCE 87

SUPPLEMENTARY 92

CONTENTS OF TABLES

Table 1. Summary for published reports examining associations between anti-HBV agents and HCC incidence or mortality 10

Table 2. Baseline characteristics of patients treated with lamivudine compared with untreated patients 38

Table 3. Hazard ratios for HCC incidence, liver-related mortality, and all causes mortality associated with lamivudine use 45

Table 4. Sensitivity analyses for HCC incidence, liver-related mortality, and all causes mortality associated with lamivudine use 47

Table 5. Baseline characteristics of patients treated with interferon or peg-interferon compared with untreated patients 49

Table 6. Hazard ratios of HCC incidence, liver-related mortality, and all causes mortality associated with interferon use 56

Table 7. Sensitivity analyses for HCC incidence, liver-related mortality, and all causes mortality associated with interferon use 58

Table 8. Information of adjuvant antiviral therapy 61

Table 9. Baseline characteristics of curative HCC patients treated with antiviral therapy compared with untreated patients 63

Table 10. Hazard ratio for HCC progression and all cause mortality, comparing untreated and treated patients 66

Table 11. Sensitivity analyses of HCC progression and all cause mortality, comparing untreated and treated patients 67

Table 12. Hazard ratio for HCC progression and all cause mortality, comparing untreated patients and patients who received adjuvant antiviral therapy at different time points 70

Table 13. Hazard ratio for HCC progression, comparing untreated patients and patients who received adjuvant antiviral therapy 80
Table 14. Hazard ratio for HCC progression, comparing untreated patients and patients who received adjuvant antiviral therapy 80

CONTENTS OF FIGURES

Figure 1. Natural progression of chronic hepatitis B virus infection.....5

Figure 2. Immortal time bias.....17

Figure 3. Study framework 21

Figure 4. Time matching analyses to control for immortal time bias 24

Figure 5. Time dependent analysis to control for immortal person-time bias 30

Figure 6. Flow diagram of study 1.....36

Figure 7. Cumulative incidence curves for HCC, liver-related death, and death from all cause associated with lamivudine use-1.....42

Figure 8. Cumulative incidence curves for HCC, liver-related death, and death from all cause associated with lamivudine use-2.....43

Figure 9. Cumulative incidence curves for HCC, liver-related death, and death from all cause associated with lamivudine use-3.....44

Figure 10. Subgroup analyses of HCC incidence, liver-related mortality, and all causes mortality for patients treated with lamivudine versus those who were not given anti-HBV treatment. 46

Figure 11. Cumulative incidence curves of HCC, liver-related death, and death from all cause associated with interferon use-1 53

Figure 12. Cumulative incidence curves of HCC, liver-related death, and death from all cause associated with interferon use-2 54

Figure 13. Cumulative incidence curves of HCC, liver-related death, and death from all cause associated with interferon use-3 55

Figure 14. Subgroup analyses of HCC incidence, liver-related mortality, and all-cause mortality for patients treated with interferon or peg-interferon versus those who were not administered anti-HBV treatment.....57

Figure 15. Flow diagram of study 2 60
Figure 16. Subgroup analyses comparing treated and untreated on HCC progression and all cause mortality of HBV-related HCC patients by adjusted hazard ratio. 68
Figure 17. Sensitivity analysis to clarify the influence of unmeasured HBV DNA level on HCC progression. 69
Figure 18. Flow diagram of replicating study 79

CHAPTER 1 BACKGROUND

Hepatitis B virus (HBV) is one of high prevalence and serious global health problem. Approximately 2 billion people have been infected, and 0.5 to 1.2 million deaths as well as 0.5 million patients of hepatocellular carcinoma (HCC) are affected by HBV each year worldwide.[1] In Taiwan, 85% to 90% general population has been infected with HBV, and the prevalence of chronic carriers is 15 to 20% of adults over 30 years of age.[2, 3] Both of liver cirrhosis (LC) and HCC are the major leading cause of death, accounting for the mortality rate being 21.4 per 100,000 and 34.9 per 100,000, respectively.[4]

To address this serious health issue, a highly effective hepatitis B vaccine was available in 1982, and since 1984 universal HBV vaccination programs for newborn babies have been launched in many countries, to control HBV infection. The infection rates of HBV have decreased worldwide. For example, in Taiwan, this program resulted in a marked decrease in the rate of HBsAg carriage from 10% in 1984 to less than 1% in 2004 and also decreased the incidence of HCC in the vaccinated cohort.[5] Despite the effectiveness of vaccination programs in many countries, the number of carriers suffering from chronic HBV infection is still approximately 240 million worldwide and 2.5 million in Taiwan.[6] These individuals are also at risk of developing liver cirrhosis (LC) and HCC; therefore, HBV control programs must be augmented by active antiviral treatment in order to decrease the risk of disease progression among patients with chronic hepatitis B (CHB).[6]

Additionally, HCC recurrence may also be attributed to viral hepatitis. Previous studies have provided evidence that HCC recurrence following curative therapy could be associated with either pathological factors related to the original tumor (accounting

for early recurrence), or persistent fibrosis and chronic hepatitis virus activity (accounting for late recurrence).[7, 8] To date, no adjuvant therapies have proven effective in preventing the early recurrence of HCC, although several clinical trials are currently ongoing.[8] Nonetheless, considering the probable cause of late recurrence, antiviral therapy may be an effective approach to inhibiting the viral and inflammatory effects which trigger hepatocarcinogenesis, potentially preventing late recurrence.[9]

Understanding of the association between hepatitis B virus and occurrence or recurrence of HCC, antiviral therapy may be an appropriate treatment for patients not only with chronic hepatitis B but also with HBV-related HCC. However, many studies investigating the ability of antiviral treatment to reduce the incidence of end-stage liver disease and mortality among CHB patients as well as to decrease the recurrence of HCC among HBV-related HCC patients following curative therapy have yielded inconsistent conclusions. The conflicting results are perhaps due to the small number of cases considered by those studies.[10-17] Therefore, this study sought to evaluate the effectiveness of antiviral therapy on occurrence and recurrence of HCC using the databases of National Health Insurance, the Taiwan Cancer Registry as well as National Death Registry to a create nationwide cohort with a large population base.

CHAPTER 2 LITERATURE REVIEW

2.1 Natural history of chronic hepatitis B

The natural history of chronic hepatitis B infection can be divided into three phases, which are based on the interaction between hepatitis B virus, host, and age at infection, including the immune tolerant phase, the immune clearance phase, and the inactive residual phase (Figure 1).

In the first phase, which is the immune tolerant phase, HBV infected persons have normal ALT level, but high HBV DNA levels (> 20,000 IU/ml), positivity of hepatitis B e antigen (HBeAg). This phase is often occurrences in persons who were infected in infant through perinatal transmission from HBeAg positive mothers and can persist for a few years to more than 30 years. This phase also has a minimal liver inflammation and injury as well as a low risk of progression to advanced liver disease.[1, 18, 19]

The second phase is immune clearance phase, which is also known as chronic hepatitis B phase or immune active phase. A large proportion (approximately 90% to 100%) of persons who were infected via perinatal route will transition into this phase between 15 and 35 years of ages. In this phase, patients' immune response against hepatitis B virus causes the rises and flared in ALT and HBV DNA levels, and seroconversion from HBeAg to anti-HBe in most persons. The estimated proportion of spontaneous of HBeAg seroconversion is 2% to 15% per year, and a small number of these patients still have active liver disease even though HBeAg is negative. Depending on the efficacy of immune system, this phase could persist for few months to years. Patients in this phase have a higher risk of liver injury and hepatic flares due to the immune response to virus.[1, 18, 19]

After HBeAg seroconversion, most patients (approximately 90%) will proceed to the third phase, which is inactive residual phase and also called immune control phase. In this phase, patients have been inactive carriers of the infection, have normal liver function, lower or undetectable HBV DNA level, and the presence of antiHBe. HBsAg seroclearance could occur in few patients at the rate of 1.0% to 1.2 % per year. A small number of these patients will develop cirrhosis and HCC. However, 2% to 3% patients per year in this phase may relapse into the second phase in which patients may be either HBeAg positive or HBeAg negative, after many years.[1, 18, 19]

Understanding the difference of three phases and the natural progression of chronic hepatitis B virus infection helps determine the treatment strategies for CHB patients. For instance, the optimal time to initiating antiviral treatment is neither in phase one nor three, which could only achieve little benefit. Furthermore, achieving HBeAg or HBsAg seroconversion as well as reducing HBV DNA to undetectable levels are defined as the surrogate endpoint or short-term aim of antiviral therapy.[1]

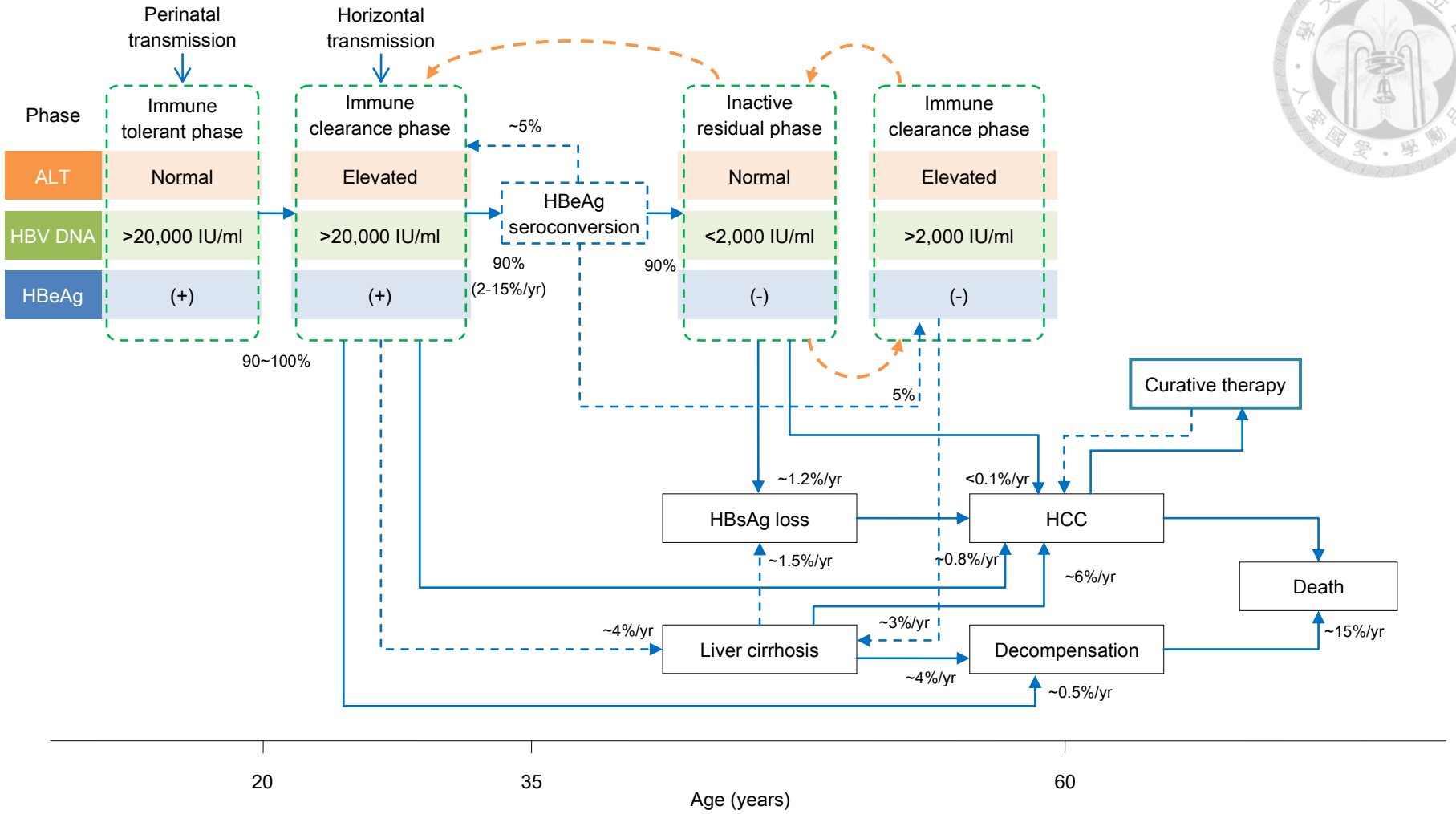


Figure 1. Natural progression of chronic hepatitis B virus infection

2.2 Antiviral therapies to prevent occurrence of hepatocellular carcinoma

2.2.1 Evolution of anti-HBV therapies

Conventional interferon (IFN) was the first antiviral therapy approved to treat patients with chronic hepatitis B in the 1980s.[6] The previous studies provided the evidence that IFN can both inhibit HBV replication and modulate host immune response. Interferon should been an ideal antiviral treatment for CHB patients in theory. However, the sustained HBeAg seroconversion rate is only 20 to 30% and the rate of undetectable HBV DNA levels at year 1 is 46 to 54% after 4 to 6 months treatment.

For convenience, conventional interferon has been expanded to pegylated interferon (PEG-IFN) in the 2000s, which is a long acting interferon. After 6 to 12 months of PEG-IFN, the short-term efficacy on sustained HBeAg seroconversion and undetectable HBV DNA levels is 30 to 35% and 63%, respectively. Even though the response rate is limited, this strategy modulates the host immune response to HBV infection, such that the treatment period is finite and post-treatment response can be maintained in more than 80% of subjects achieving serologic responses.[1] Nonetheless, there are a number of disadvantages associated with interferon-based treatment strategies. For example, IFN-based therapy requires a subcutaneous injection and has been associated with various adverse effects. Therefore, this type of therapy is used to treat fewer than 5% of cases worldwide.

Since 1998, the other classes of antiviral agents, which were oral nucleoside or nucleotide analogues, have licensed for anti-HBV treatment. Currently, there are five nucleos(t)ide analogues (NAs) approved to treat chronic HBV including lamivudine, adefovir, entecavir, telbivudine and tenofovir.[1, 6] In contrast to interferon therapy,

NAs only target HBV replication and advocate maintenance antiviral therapy over an indefinite period, until HBsAg clearance. These drugs are relatively easy to administer, present a low risk of adverse events, and have no contraindications. Thus, these agents are commonly used.

Lamivudine is the first historical drug of these agents, and is as effective as IFN-based treatment in HBeAg seroconversion and suppressing HBV DNA. The short-term efficacy on sustained HBeAg seroconversion and undetectable HBV DNA levels is 20% and 40 to 72% at year 1, respectively. However, this drug is the most frequently occurring drug resistance, accounting for the resistant rate being 57% and 69% after 3 and 5 year of lamivudine therapy. In 2005, entecavir was approved as first-line antiviral treatment for CHB patients and treatment for lamivudine-resistant CHB patients. Because of the higher rate of virological suppression and lower rate of drug resistance, entecavir has become as the first choice of NAs for treating CHB patients.[1, 6]

2.2.2 Specific intervention

Previous studies have provided considerable evidence to support an association between HBV replication and the progression of liver disease. Based on this result, the short-term aim of antiviral therapy is to achieve HBeAg or HBsAg seroconversion or to reduce HBV DNA to undetectable levels.[1] These regimens further seek to prevent the development of HCC and to extend patient survival. The long-term effectiveness of antiviral therapies for chronic hepatitis B patients have been widely studied (Table 1).

To the best of our knowledge, the most common antiviral therapy to be investigated was conventional interferon. Two randomized controlled trials and several clinical observational studies with a median of 6 to 8 years of follow-up have evaluated the efficacy in reducing the incidence of HCC or death. However, due to inconsistent results, this issue remains a matter of contention.[10-12, 20-29] The fact that previous studies were hampered by small sample sizes (approximately: 100 to 500 patients) and limited statistical power has necessitated a nationwide study with a large population base.

The efficacy of anti-viral nucleos(t)ide analogues (NAs) in reducing the incidence of HCC or death has also been demonstrated in previous studies. For example, the well-known CALM study was the first to show that maintenance LAM treatment was effective in reducing HCC incidence in patients with advanced fibrosis or compensated cirrhosis.[30] Consistent with results from CALM study, three observational studies were also shown to be effective in lamivudine treatment at decreasing HCC incidence and mortality among CHB patients.[31-34] Recent studies on maintenance therapy using new antiviral NAs (such as entecavir) also reported a

reduction in HCC incidence.[35, 36] Overall, these results pertaining to the efficacy of anti-viral NAs in improving long-term outcomes are quite convincing. However, in the past, efficacy has mostly been demonstrated for the period in which maintenance therapy was administered, or within a short time frame (1 or 2 years) following the cessation of NAs therapy. How long this efficacy could last following the cessation of therapy remains unclear.

Table 1. Summary for published reports examining associations between anti-HBV agents and HCC incidence or mortality

Study/Year	RCT	N(treatment vs. Control)	HBeAg(+) (%)	HCV (%)	Cirrhosis (%)	Age (Median or Mean)	Gender (Male %)	Treatment duration (Months)	Follow-up (Years)	Outcome	
										HCC (%)	Death (%)
Interferon vs. No treatment											
Fattovich/1997 [20]	N	90 (40 vs. 50)	100.0 vs. 100.0	0.0	100.0	47 vs. 45	85.0 vs. 88.0	1-13	7.2	10.0 vs. 12.0	20.0 vs. 28.0
Ikeda/1998 [21]	N	313 (94 vs 219)	64.9 vs. 45.2	0.0	100.0	41 vs. 44	83.0 vs. 76.7	10	7.0	10.6 vs. 23.3	NA
Benvegnu/1998 [22]	N	37 (13 vs. 24)	NA	24.3	100.0	57 vs. 60	NA	4-6	6.0	7.7 vs. 29.1	0.0 vs. 20.8
Brunrtto/1998 [23]	N	146 (49 vs. 97)	NA	0.0	100.0	54 vs. 54	NA	7	5.8	16.0 vs. 19.0	NA
Kroqsqaard/1998 [24]	N	308 (210 vs. 98)	100.0 vs. 100.0	NA	6.1	24.5	55.2	NA	4.7	1.0 vs. 1.0	2.9 vs. 4.1
Di Marco/1999 [25]	N	302 (109 vs 193)	32.1 vs. 26.4	14.2	28.5	33 vs. 35	66.1 vs. 26.4	NA	7.8	1.8 vs. 3.1	6.4 vs. 14.5
Mazzella/1999 [26]	Y	64 (33 vs. 31)	100.0 vs. 100.0	10.9	0.0	36 vs. 41	75.8 vs. 80.6	6	7.2	3.0 vs. 6.5	NA
Lin/1999 [27]	Y	101 (67 vs. 34)	100.0 vs. 100.0	0.0	11.9	32 vs. 32	100.0 vs. 100.0	NA	8.2	1.5 vs. 11.8	1.5 vs. 11.8
Papatheodoridis/2001 [12]	N	404 (209 vs. 195)	0.0 vs. 0.0	0.0	30.9	47 vs. 49	83.3 vs. 82.1	6 or 12	6.0	8.1 vs. 7.7	8.6 vs. 10.8
Tangkijvanich/2001 [28]	N	139 (67 vs. 72)	100.0 vs. 100.0	0.0	20.1	37 vs. 40	79.1 vs. 65.3	4-6	5.0	3.0 vs. 12.5	NA
Yuen/2001 [11]	N	411 (208 vs. 203)	100.0 vs. 100.0	0.0	NA	27 vs. 28	71.2 vs. 57.1	3-6	8.9	2.9 vs. 0.0	NA
Truong/2005 [29]	N	62 (27 vs. 35)	100.0 vs. 100.0	0.0	1.6	31.5	53.2	1-6	6.5	3.7 vs. 0.0	NA
Lin/2007 [10]	N	466 (233 vs. 233)	100.0 vs. 100.0	0.0	9.4	32 vs. 31	94 vs. 94	3-7	6.5	2.1 vs. 6.9	NA
Lamivudine vs. No treatment											
Liaw/2004 [30]	Y	651 (436 vs. 215)	58.0 vs 58.0	0.0	61.3	43 vs. 44	85.0 vs. 85.0	32.4	2.7	3.9 vs. 7.4	0.0 vs. 0.0
Matsumoto/2005 [31]	N	2795 (657 vs. 2138)	54.0 vs. 59.5	0.0	15.3	41 vs. 37	76.6 vs. 74.0	18.9	5.9	4.7 vs. 11.2	NA
Papatheodoridis/2005 [32]	N	396 (201 vs. 195)	0.0 vs. 0.0	0.0	33.3	52 vs. 49	83.1 vs. 82.1	48.0	3.8	2.5 vs. 7.7	4.5 vs. 10.8
Yuen/2007 [33]	N	266 (142 vs. 124)	100.0 vs. 100.0	0.0	0.0	34 vs. 33	74.6 vs. 72.6	60.0-96.0	8.2	0.7 vs. 2.4	NA
Eun/2010 [34]	N	1571 (872 vs. 699)	79.6 vs. 91.1	0.0	42.8	40 vs. 36	69.3 vs. 73.2	>12	4.1	6.7 vs. 9.9	NA
Entecavir vs. No treatment											
Hosaka/2013 [35]	N	1615 (472 vs. 1143)	46.0 vs. 35.0	0.0	19.0	47 vs. 39	66.7 vs. 63.0	NA	5.4	2.5 vs. 12.6	NA
Wong/2013 [36]	N	1890 (1466 vs. 424)	30.0 vs. 37.0	0.0	29.2	51 vs. 41	72.0 vs. 65.0	>12	6.3	3.7 vs. 12.5	2.6 vs. 14.2

2.2.3 Reimbursement under the Taiwan National Health Insurance program for antiviral therapy for hepatitis B virus

Considering the high prevalence and serious health outcome of HBV, on October 1 2003, the National Health Insurance (NHI) Administration in Taiwan initiated a chronic hepatitis B virus treatment program, which reimbursed finite-period antiviral treatments for active CHB patients. In the beginning of program execution, the first-line antiviral agents were comprised conventional interferon (IFN) and lamivudine (LAM). These agents were updated to include peg-interferon (PEG-IFN) in November 2005, entecavir (ETV) and telbivudine (LdT) in August 2008, as well as tenofovir (TDF) in July 2010.

Between October 2003 and October 2009, the reimbursement criteria were as follows. HBeAg-positive CHB patients: (1) single serum ALT level equals to or greater than 5 times the upper normal limit; (2) repeated serum ALT levels equal to or greater than 2 times the upper normal limit, three months apart. HBeAg-negative CHB patients: (3) repeated serum ALT levels equal to or greater than 2 times the upper normal limit, three months apart. Patients who met criteria (2) or (3) prior to the implementation of the reimbursement program were required to have detectable hepatitis B core antigen (HBcAg), according to immunohistochemical staining in the liver biopsy specimens.

The treatment period for these antiviral agents differed. Patients were eligible to receive IFN therapy for a period of 4 to 6 months (extended to 6 to 12 months on November 2009), PEG-IFN therapy for a period of 6 to 12 months, or nucleos(t)ide analogues (NAs) for a period of 12 to 18 months (extended to 12 to 36 months on November 2009).

2.3 Adjuvant antiviral therapy to prevent recurrence of hepatocellular carcinoma

Curative therapies such as surgical resection, percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA), are regarded as first-line treatments for early stage HCC capable of increasing the duration of overall survival and disease-free status.[37-39] Nonetheless, no matter how effective curative therapies may be, HCC still commonly recurs following the administration of curative therapies. A review article which summarized clinical trials and observational studies reported that the 3-year and 5-year recurrence rates of liver cancer were approximately 20% to 50% and 50% to 79%, respectively.[37] These recurrences also affected the overall survival rate of patients. Clearly, lowering the rate of recurrence following the administration of curative therapies is a crucial step toward the further improvement of treatment for HCC.

Several common adjuvant therapies for solid organ cancers, such as systemic chemotherapy, immunological therapy, immunochemotherapy, radiotherapy, and retinoid therapy, have been evaluated the efficacy on reduction of HCC recurrence in clinical trials. However, the results of these studies are conflicting and have failed to prove effective in preventing the recurrence of HCC.[8, 40, 41] Considering the association between hepatitis B virus and late recurrence, antiviral therapy is regarded as a possible approach in preventing late recurrence by inhibiting the viral and inflammatory effects.[9]

To the best of our knowledge, interferon (IFN) treatment was the first historical and the most common antiviral therapy to be administered to viral hepatitis-related HCC patients. However, HBV patients were included in only a few studies [42] and three large randomized clinical trials did not document the effectiveness of treatment on

HBV patients.[43-45] Current standardized care for chronic hepatitis B has been expanded to include nucleoside or nucleotide analogs and pegylated interferon.[46] The efficacy of these updated antiviral agents in reducing the rate of recurrence among HBV-related HCC patients following curative therapy remains a matter of contention.[13-17] Previous research investigating nucleoside analogue therapy, including lamivudine or entecavir, has yielded inconclusive results. Three observational studies supported a decrease in overall mortality or HCC recurrence [17, 47, 48]; however, other studies did not.[13, 14] It is possible that the inconsistent results would be due to limited statistical power in those studies.

A recent nationwide study reported that use of nucleoside analogues is associated with a protective effect against HCC recurrence among patients who received liver resection in Taiwan.[49] However, several issues in the previously mentioned study are in need of further clarification before a definite conclusion can be reached. For example, this study had limited information about liver cancer status and whether therapeutic cure. Certain liver cancer status and whether therapeutic cure are inherently associated with a decision of receiving adjuvant antiviral therapy and a risk of HCC recurrence and mortality.[50, 51]

Moreover, the effects of starting adjuvant antiviral therapy at different time-points following curative treatment for HCC have yet to be investigated. Prior studies which reported the benefits of antiviral therapy found that the average time between initiation of antiviral therapy and first-line HCC treatment was approximately 2 months.[16, 17, 47] However, studies of null association indicated no clear time-point for the initiation of adjuvant antiviral therapy.[13-15] Thus, evidence indicating the start time of this treatment influences survival outcomes is limited.

2.4 Biases in retrospective cohort studies based on secondary databases

Using secondary databases to investigate the effectiveness study has provided the additional information of treatments in real-world clinical practice. However, this evidence is still controversial due to potential error which may confound the validity of effect estimate. Illustrating the potential biases and applying proper research design as well as analytic approach can be eliminated or minimized the influence of biases. We will try to identify biases in cohort study and discuss the appropriate approaches to prevent.[52, 53]

The potential biases in retrospective cohort studies based on secondary databases occur at many points along the research process. In identifying study participants, confounding is the first question to be addressed. For example, we always used diagnosis of specific disease to define the target population. Even if patients have the same diagnosis of disease, their disease severity would be very different. Restricting study cohort meeting inclusion and exclusion criteria can reduce this bias and lead to similar participants, particularly when the variables would influence the effect estimate but can not be able to adjust in the analysis.[52] New (incident) user design which establishes an inception cohort for effectiveness study is another approach to deal with confounding factors from the exposure group.[54] This design can make the treatment groups homogeneous in baseline characteristics.

In addition, the researcher can reduce confounding through another analytic approaches such as adjustment, or stratification. Propensity score (PS) is an efficient way by using logistic regression to estimate the probability of each patient receiving treatment on the basis of confounding factors and is employed PS adjustment, PS matching, PS stratification and inverse probability of treatment weighting (IPTW) to

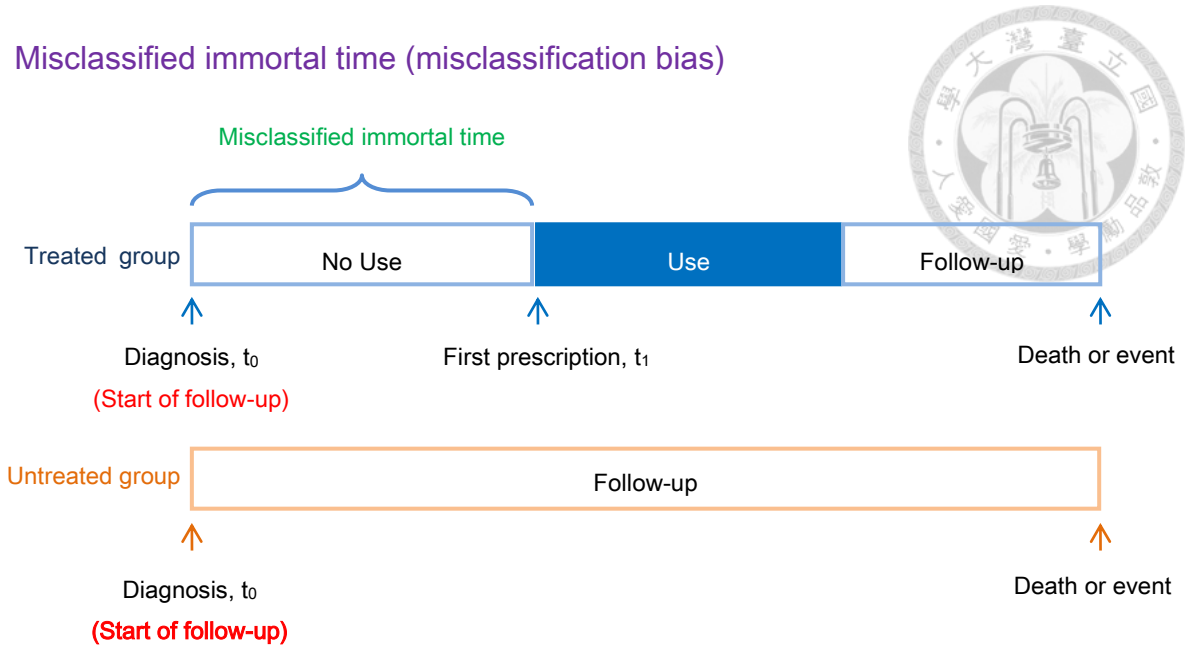
adjust, compare or create a cohort of patients who shared similar observed characteristics.[55]

When the classification of treated patients who have lived until the date of receiving treatment after the start of follow-up, immortal time bias would be introduced. Immortal time bias is included misclassified immortal time which incorrectly defined the time of exposure as well as excluded immortal time which excluded the period between the start of follow-up and the start of receiving treatment, but introduced selection bias (Figure 2).[56] Previous studies have shown that results can be biased by either misclassified immortal time or excluded immortal time in favor of treatment with a shift in the estimation toward protective.[57] To ensure that immortal person-time bias was not introduced by treated patients, analyses were incorporated as a time-dependent exposure which correctly identified the time of treatment or accomplished using time matching to create a sub-cohort of treated patients and untreated patients which reduced selection bias.[58]

During the follow-up period, treated patients may have been discontinued, added or switched to other agents due to lack of effect or early sign of an adverse event. Because this phenomenon is dependent, this censoring is known as informative censoring (which does not include competing risk). To assess effectiveness of the main drug exposure of interest, an as-treated (AT) analysis which censors patients at the exposure window ends, is the most common way. However, censoring in survival analysis should be not related to the study, which is known as random or non-informative censoring. Using as-treated analysis which assumed that patients are lost to follow-up at random may have led to bias in the estimation of effectiveness due to informative censoring. One approach to address the problem of informative

censoring is inverse probability of censoring weighting (IPCW).[59] The other approach is that using both of as-treated (AT) analysis and first-exposure-carried-forward analysis to present treatment effectiveness. The first-exposure-carried-forward (FECF, i.e., intention-to-treat analysis) was performed, in which the treatment group was identified according to the first prescription of antiviral therapy, disregarding changes or additions to the drug regimen. The use of first-exposure-carried-forward analysis may have led to bias toward the null due to the misclassification of exposure. Although the AT and FECF showed separately will introduce biases, the use of both these made it possible to indicate a potential range of effectiveness.[54]

Even though secondary database provided a lot of information about medical behaviors, some critical clinical parameters related to the adoption of treatments and study outcomes such as biological or virological data, could not be obtained from the study database, particularly in claims database. These factors are regarded as unmeasured confounding factors. To establish the influence and estimate the true effect after adjusting unmeasured confounding factors, sensitivity analyses included rule-out approach and array approach are assessed by applying predefined analyses.[60]



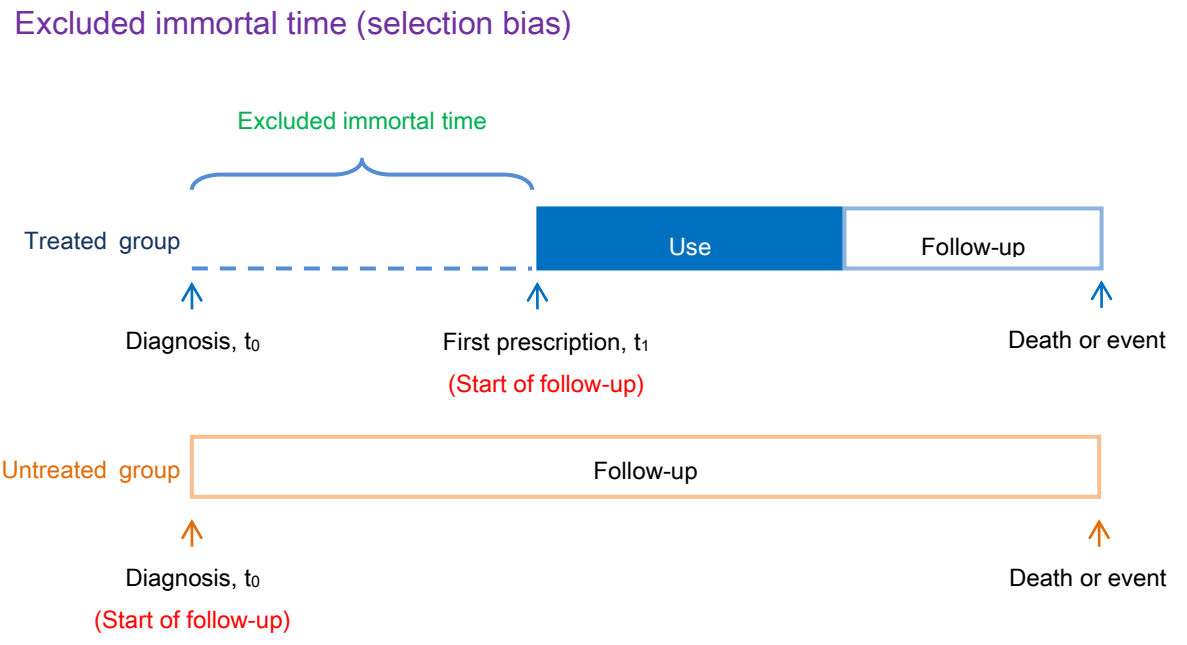


Figure 2. Immortal time bias

2.5 Summary

Because of high prevalence and serious health impact of chronic hepatitis B virus, antiviral therapy have been launched to inhibit occurrence of HCC among CHB patients and recurrence of HCC among HBV-related HCC patients. Although many studies have investigated the effectiveness of antiviral therapy, there are still several limitations in these studies which are needed to be addressed.

Gap of current evidence

First, the long-term effectiveness of IFN therapies have been widely studied among chronic hepatitis B patients; however, because of limited sample size, the results of these studies are conflicting. Second, maintenance anti-viral nucleos(t)ide analogues (NAs) in reducing the incidence of HCC or death are quite convincing. Nonetheless, the long-term effects of finite-period nucleos(t)ide analogues have yet to be investigated. Third, the efficacy of adjuvant antiviral agents (including IFN and NAs) in reducing the recurrence rate among HBV-related HCC patients following curative therapy remains a matter of contention. Even though a recent nationwide study reported that use of nucleoside analogues is associated with a protective effect against HCC recurrence among patients who received liver resection, the limited information about liver cancer status and whether therapeutic cure in this study would be probably to confound results by biasing the effect estimate towards a protective effect. Fourth, the effects of starting antiviral therapy at different time-points following curative treatment for HCC have yet to be investigated.

On October 1, 2003, the Bureau of National Health Insurance (NHI) in Taiwan initiated a CHB treatment program, which reimbursed CHB patients for antiviral treatments. Considering sample size of study participants and period of follow-up, this

study sought to evaluate the long-term effectiveness of lamivudine or interferon/peg-interferon on HCC development and mortality. This study was also to investigate the effect of adjuvant antiviral therapies on HBV-related HCC progression and deaths in patients receiving curative treatment based on clear clinical-pathological cancer status, and the association of start time of adjuvant antiviral therapy initiation and outcomes.

CHAPTER 3 STUDY AIM AND FRAMEWORK

3.1 Study aim

This study sought to use secondary database to establish retrospective CHB or HBV-related HCC cohorts to evaluate the long-term effectiveness of antiviral therapy on occurrence or recurrence of HCC. Two parts of studies were as follow:

Study 1: Effectiveness research of lamivudine or interferon/peginterferon in chronic hepatitis B patients

(1) Using occurrence of HCC and mortality as outcome variables to evaluate the long-term effect of lamivudine or interferon/peg-interferon among patients with HBV infection

Study 2: Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment

(1) Using HCC progression and mortality as outcome variables to evaluate the effect of adjuvant antiviral treatment among HBV-related HCC patients

(2) Evaluating the association of start time of adjuvant antiviral therapy initiation and outcomes

3.2 Study framework

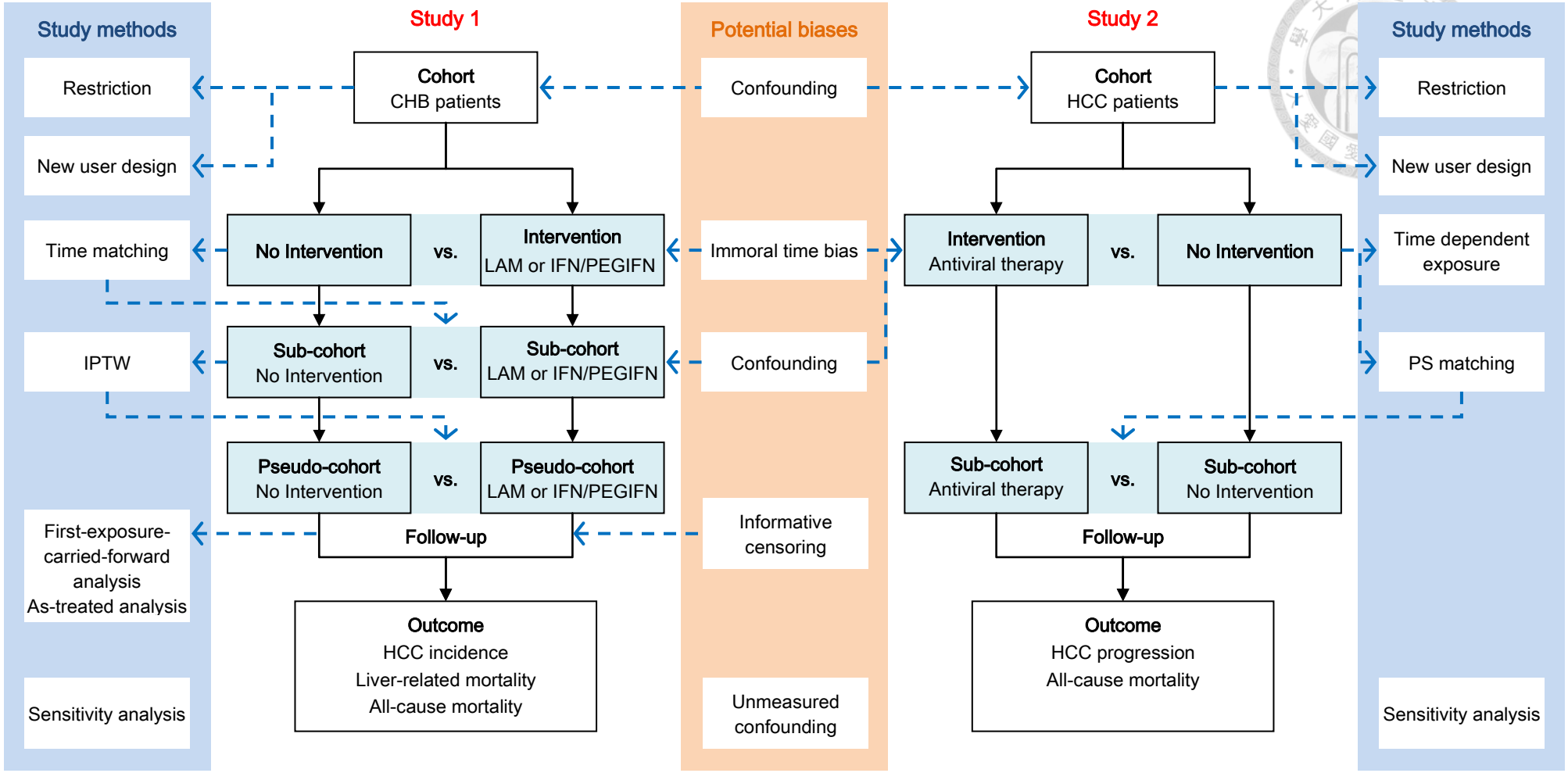


Figure 3. Study framework

Study 1: Effectiveness research of lamivudine or interferon/peg-interferon in chronic hepatitis B patients

Study 2: Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment

CHAPTER 4 MATERIALS AND METHODS

4.1 Effectiveness research of lamivudine or interferon/peginterferon in chronic hepatitis B patients

Data Sources

Patients who met study criteria were identified from the National Health Insurance (NHI) program, a mandatory single-payer health insurance system covering outpatient and inpatient services provided by both the private and public sectors. At the end of 2011, approximately 99.6% of the Taiwanese population (23 million) was insured under this program.[61] The NHI database includes demographic characteristics, prescription drug use, and disease record.

Information related to disease outcomes was linked to a national registry to determine the incidence of HCC and death. The incidence of HCC was obtained from the Taiwan Cancer Registry Database, which collects information from all newly diagnosed cancer patients treated in hospitals with a capacity exceeding 50 beds.[62] The date and cause of death was obtained from the National Death Registry database.

Study Population

Retrospective cohort with CHB patients

We conducted a nationwide retrospective cohort study by identifying patients diagnosed with chronic hepatitis B (CHB) (ICD-9-CM: 070.2, 070.3, V026.1) between January 1, 2004 and December 31, 2010. Diagnosis of CHB was verified according to claims data of hepatitis B carriers as well as a record of having received an alanine aminotransferase (ALT) test at least twice during one year. In addition,

CHB patients were excluded from the study if they met any of the following criteria: (1) aged <18 years or were missing information on gender; (2) suffering from co-infection with chronic hepatitis C (CHC) or human immunodeficiency virus (HIV); (3) diagnosed with any form of cancer within the year prior to enrollment; (4) received anti-HBV therapy within the year prior to enrollment; (5) received antiviral agents other than lamivudine, interferon, or peg-interferon as first-course of antiviral therapy; (6) received multiple anti-HBV medicines as first prescription; (7) received the first prescription of anti-HBV therapy during hospitalization. When estimating the effectiveness of IFN or PEG-IFN therapy, patients with any evidence of liver decompensation within one year prior to enrollment or anti-HBV treatment were also excluded due to a contraindication against the use of IFN and PEG-IFN therapy.

Intervention group

Drug intervention was defined as the first prescription of a target anti-HBV agent, between January 1, 2004 and December 31, 2010, following the second ALT test. Patients who received at least one prescription for target anti-HBV agents were selected in the intervention group and those who received the target anti-HBV agents were listed in the two group including lamivudine and interferon/peg-interferon.

We determined the total duration of antiviral therapy use by calculating the number of days each drug was prescribed.

Comparison group

Patients, who did not receive any anti-HBV agent between January 1, 2004 and December 31, 2010, following the second ALT test, were identified as a comparison group. However, because intervention group who, after receiving an ALT test, had

survived until receiving antiviral therapy, compared with untreated patients, this will introduce immortal time bias. To accomplish this, we used time matching to create a sub-cohort of intervention group who received lamivudine, interferon, or peg-interferon as well as a sub-cohort of comparison group.[58] Time distribution was calculated from the date of the second ALT test to the date of the first antiviral prescription using individual patients from the intervention group randomly matched with up to 10 comparison patients (a 1:10 ratio). Patients were matched according to the date of second ALT test ± 7 days, gender, and age group. The comparison patients were assigned the same index date as that of the matched intervention patients. Consequently, comparison patients who underwent an event prior to the index date were excluded (Figure 4).

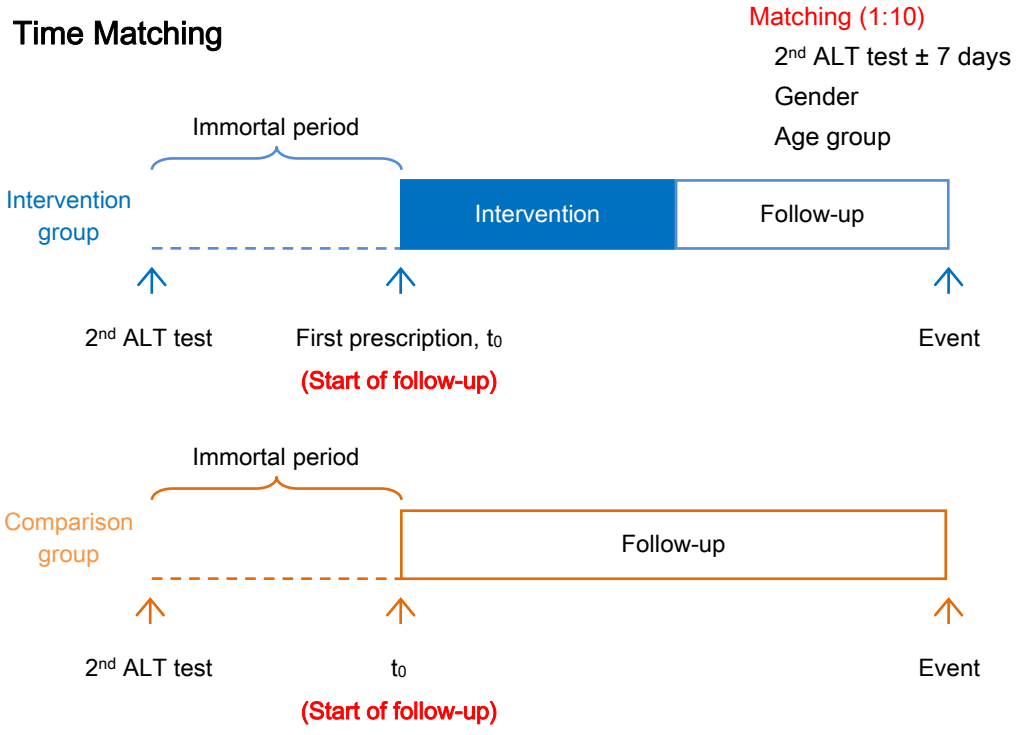


Figure 4. Time matching analyses to control for immortal time bias

Outcome Ascertainment

Three outcomes were assessed. The primary outcome was the incidence of HCC, which was determined using the Taiwan cancer registry database. The secondary outcomes were liver-related mortality and all-cause mortality, which were determined using data from the NDR database in Taiwan. Liver-related death was designated by ICD-9 codes 070, 155, 456, 570, 571, 572, or 573, and by ICD-10 codes B15-19, C22, I 85, or K70-76.[63] All patients were followed up until the development of HCC, death, or December 31, 2010.

Potential Confounding Factors and Propensity Score Models

This study included the following variables in analyses: sex, age, comorbidities, presence of liver disease, severe complications resulting from liver disease or hospitalization and emergency department visits for liver disease. We identified comorbidities using Deyo's Charlson Comorbidity Index as described by Quan et al.[64] Specifically, we considered liver diseases including alcoholic liver disease (ICD-9-CM codes: 571.0-571.3), cirrhosis of the liver without mention of alcohol (ICD-9-CM codes: 571.5-571.6), as well as severe complications of liver disease including ascites (ICD-9-CM codes: 789.5), hepatic encephalopathy (ICD-9-CM codes: 572.2), esophageal varices (ICD-9-CM codes: 456.0-456.2), and hapatorenal syndrome (ICD-9-CM codes: 572.4) diagnosed within one year prior to the index date. Information was obtained from the NHI database, and all diagnoses were identified from a single report in inpatient files or not less than 2 reports in outpatient files.

All confounding factors were adjusted through propensity score methods, which estimated the probability of each patient receiving antiviral therapy on the basis of confounding factors. In order to assemble groups of comparable patients, we

employed inverse probability of treatment weighting (IPTW) to create a pseudo population.[65]

Subgroup Analyses

To further determine the effectiveness for these subsets of cohorts, analysis was stratified using the variables of sex, age, and the presence or absence of alcoholic liver disease, cirrhosis, diabetes, and renal disease.

Hypothesis Testing

1. Intervention group presented a lower risk of HCC incidence, liver-related mortality and all-cause mortality, compared to the comparison group

2. No difference in long-term effectiveness of antiviral therapy between all of subgroup.

Statistical Analysis

The degree of balance in measured covariates was compared between groups using standardized differences in which a difference of less than 0.1 was adopted as an indicator of good balance within the cohort.[66] Outcomes were compared using a Cox proportional hazard model to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CI). Because using IPTW to create a pseudo population could lead a single patient included multiple times, robust variance estimation via Cox proportional hazard model was used.[67]

However, intervention patients could be added or switched to other anti-HBV agents in the follow-up period due to drug resistance or HBV relapse. Hence, primary and secondary analyses were performed as follows: (1) primary analysis

(first-exposure-carried-forward), in which the treatment group was identified by the first prescription of antiviral therapy, ignoring changes or additions to the other drug regimen; (2) secondary analysis (as-treated), in which patients were censored from the date at which the anti-HBV drug regimen was altered.[54] In addition, we also try to employ inverse probability of censoring weighting (IPCW) to address the problem of informative censoring.[59]

All analyses were two-sided, and *p* values smaller than 0.05 were considered statistically significant. Statistical analyses were performed using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Sensitivity Analyses

To assess the robustness of our findings, all groups were analyzed using standardized mortality ratio (SMR) weighting [68], propensity score matching and multivariable adjustment in sensitivity analysis.

4.2 Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment

Data sources

We conducted a nationwide inception cohort study by identifying HCC patients from the Taiwan Cancer Registry Database. The Taiwan Cancer Registry collects information from all newly diagnosed cancer patients treated in hospitals with a capacity greater than 50 beds.[62, 69] All hospitals which are major providers of cancer care have been eligible to report to the Long-Form database of the Taiwan Cancer Registry (LF-TCR) since 2002. LF-TCR data includes demographics, clinico-pathological variables, and information related to the first course of HCC treatment. Approximately 81.5% of patients newly diagnosed with HCC were listed in the LF-TCR between 2005 and 2009.[39]

In addition, we obtained complete treatment and disease records from the claims database of the National Health Insurance (NHI) program as well as information regarding the date and cause of death from the National Death Registry (NDR) database.

Study population

Retrospective cohort with HCC patients

We conducted a nationwide retrospective cohort study by identifying patients who were first diagnosed with HCC (ICD-O-3: C220) between January 1, 2004 and December 31, 2010. To meet inclusion criteria for this study, patients also had to have been diagnosed with viral hepatitis B (ICD-9-CM: 070.2, 070.3, V026.1) within 1 year of receiving a liver resection, PEI, or RFA as the first course of HCC treatment.

Additionally, patients were excluded if they met any of the following criteria: (1) diagnosed with another primary form of cancer between 2004 and 2010; (2) aged < 18 years; (3) suffered from co-infection with HBV and HCV; (4) received combination treatment as first-line cancer therapy; (5) possessed an unclear surgical margin; (6) received antiviral therapy before first-line treatment for HCC; (7) suffered from a tumor that had directly invaded adjacent organs or lymph nodes, or had undergone distant metastasis as defined by the American Joint Cancer Committee on Cancer (AJCC) system, 6th edition.[70]

Among all eligible patients, 93.6% whose NHI claims data for the first course of HCC treatment corresponded to LF-TCR records (resection group: 97.3%; PEI group: 83.2%; RFA group: 79.5%), were selected for the final analysis.

Intervention group

The main drug exposures of interest were the antiviral therapies: lamivudine, entecavir, adefovir, telbivudine, entecavir, tenofovir, interferon and pegylated interferon. Patients who received at least one prescription for any antiviral medication were categorized as an intervention group. To investigate the relationship between the start date of antiviral therapy and the risk of HCC progression, intervention patients were further subdivided into 4 groups according to the interval between curative treatment and initiation of adjuvant antiviral therapy: <6 months, 6-12 months, 12-24 months, and >24 months. Index date was defined as the starting date of the first course of HCC treatment.

We determined the total duration of antiviral therapy use by calculating the number of days each drug was prescribed.

Comparison group

Patients, who did not receive any anti-HBV agent between January 1, 2004 and December 31, 2010, were identified as a comparison group. To ensure that immortal time bias was not introduced by intervention patients who lived until receiving antiviral therapy after the first course of treatment for HCC, antiviral therapy was incorporated as a time-dependent variable, in which intervention patients in the period between the first course of treatment for HCC and the first prescription of antiviral therapy were regarded as comparison group (Figure 5). [56, 57]

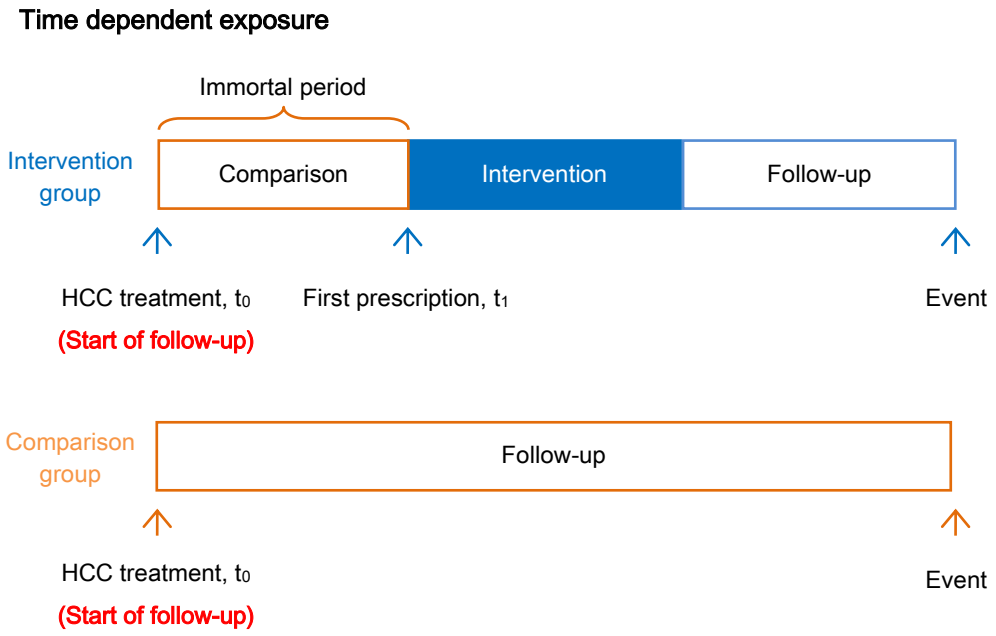


Figure 5. Time dependent analysis to control for immortal person-time bias

Outcome Ascertainment

We assessed two outcomes. The first was HCC progression, which was followed patients received second-line cancer therapy (i.e. surgery, RFA, PEI, trans-arterial

embolization [TAE], trans-arterial chemoembolization [TACE], radiotherapy, chemotherapy, or hormonal therapy) or died from all causes. The second outcome considered the all-cause mortality, which were followed patients until to the date of death. All patients were followed up until the initiation of second-line HCC treatment, death, or December 31, 2011.

Potential Confounding Factors and Propensity Score Models

We included the following variables in our analyses: sex, age, clinical stage and type of first course of HCC treatment which was obtained from the LF-TCR database. In addition, we defined comorbidities using Deyo's Charlson Comorbidity, which had to have been diagnosed within 1 year prior to the index date.[64] Furthermore, to evaluate the liver status of patients, the presence of liver diseases, including alcoholic liver disease and cirrhosis of the liver without mention of alcohol, were also identified. These conditions had to have been diagnosed within 1 year of the index date. We also considered severe complications of liver disease, including ascites, hepatic encephalopathy, esophageal varices, and hapatorenal syndrome provided they had been diagnosed within 1 year posterior to the index date. Information was obtained from the NHI database and all diagnoses were identified from a single report in inpatient files or not less than 2 reports in outpatient files.

We used propensity score methods to create a cohort of matched patients who shared similar observed characteristics. We calculated propensity scores using logistic regression to estimate the probability of each patient receiving antiviral therapy on the basis of confounding factors. Patients with calipers of less than 0.2 standard deviations of the logit of propensity scores were grouped together. The matched cohorts were an attempt to group each patient who received antiviral therapy with up

to 4 patients who did not (a 1:4 match).[55]

Subgroup Analyses

Analyses were stratified by variables of sex, age, tumor status, type of HCC treatment, as well as the presence or absence of alcoholic liver disease, cirrhosis and DM to further determine the effectiveness of adjuvant antiviral therapy for this subset of cohorts.

Hypothesis Testing

1. Intervention group presented a lower risk of HCC progression and all-cause mortality, compared to the comparison group
2. No difference in effectiveness of antiviral therapy between all of subgroup.
3. No association of start time of adjuvant antiviral therapy and HCC progression

Statistical Analysis

The degree of balance in measured covariates was compared using the Mantel-Haenszel test for categorical variables and generalized estimating equations (GEE) regression for continuous variables. We also calculated standardized differences to obtain a balance between the treated and untreated groups, adopting a difference of less than 0.1 as an indicator of good balance in the matched cohort. Outcomes were compared using a Cox proportional hazard model to estimate the adjusted hazard ratio (HR) and 95% confidence intervals (CI). To estimate treatment effect based on matched cohort, Cox proportional hazard models were used a robust variance estimator accounting for the clustering within matched pairs as well as stratified on matched pairs, separately.[18, 19] To ensure that immortal person-time

bias was not introduced by treated patients who lived until receiving antiviral therapy after the first course of treatment for HCC, antiviral therapy was incorporated as a time-dependent variable. All analyses were two-sided, and *p* values smaller than 0.05 were considered statistically significant. Statistical analysis was performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Sensitivity Analyses

Several sensitivity analyses were conducted to assess the robustness of our findings. To improve the validity of our definition for curative HCC therapy, we used the same approach to examine the subset of patients who were alive with cancer-free status at least one year after the index date, the subset of provided they underwent a liver resection and had a clear surgical margin, and the subset of both criteria.

In addition, because one of recommended indications of antiviral therapy is high HBV DNA level, patients in treated group may probably have higher rate of high HBV DNA level then untreated group. High HBV DNA level is also a risk factor of HCC recurrence. However, information about HBV DNA level was not obtained from our database. To clarify the influence of unmeasured HBV DNA level on HCC progression, we conducted another sensitivity analysis which bases on the an array informed assumption.[60]

- Sensitivity analysis - array approach

$$ARR = \mathrm{RR} \times \frac{\mathrm{P_{C1}}\,(\mathrm{RR_{CD}} - 1) + 1}{P_{C0}\,(\,RR_{CD} - 1) + 1}$$

RR: ‘True’ or fully adjusted exposure relative risk

ARR: Apparent exposure relative risk

RR_{CD}: Association between confounder and disease outcome

PC: Prevalence of confounder

PC_1: Prevalence of confounder in the exposed

PC_0: Prevalence of confounder in the unexposed

We defined that the association with high HBV DNA level ($>10^6$ copies/ml) and HCC recurrence was 2.55 times compared with low HBV DNA level ($\leq 10^6$ copies/ml).[71] Given that the prevalence of high HBV DNA level ($>10^6$ copies/ml) in HBV-related HCC patients was 43% and the prevalence in untreated patients may be probably lower than those patients [71], we assumed that the prevalence of high HBV DNA level in untreated patients would be ~30%.

CHAPTER 5 RESULTS

5.1 Effectiveness research of lamivudine or interferon/peginterferon in Chronic Hepatitis B patients

Cohort Selection

The NHI database includes a total of 630,405 patients diagnosed with chronic hepatitis B between January 1, 2004 and December 31, 2010. Among these patients, only 464,452 patients fulfilled inclusion criteria of routine ALT test. We also excluded 2,858 patients who have missing information of gender; 2,584 patients who were less than 18 years old; 19,253 patients who were co-infected with HCV or HIV; 36,139 patients who were diagnosed any kinds of cancer before enrollment; 5,598 patients who have received antiviral therapy before enrollment; 17,742 patients who did not received lamivudine, interferon or peg-interferon mono-therapy as the first prescription of antiviral therapy; 4,879 patients who received the first prescription of antiviral therapy during hospitalization. Finally, 375,399 CHB patients met the inclusion and exclusion criteria, including 361,299 untreated, 11,314 with lamivudine, and 2,786 with interferon or peg-interferon (Figure 6). As previously noted, a large number of CHB patients in many other countries do not receive treatment due to limited accessibility or a lack of awareness on the part of patients or physicians.

Following matching based on prescription time distribution, the matched cohort of lamivudine with untreated patients included 103,160 patients. After excluding 896 patients with records of liver decompensation, the matched cohort of interferon or peg-interferon with untreated patients included 25,919 patients (Figure 6).

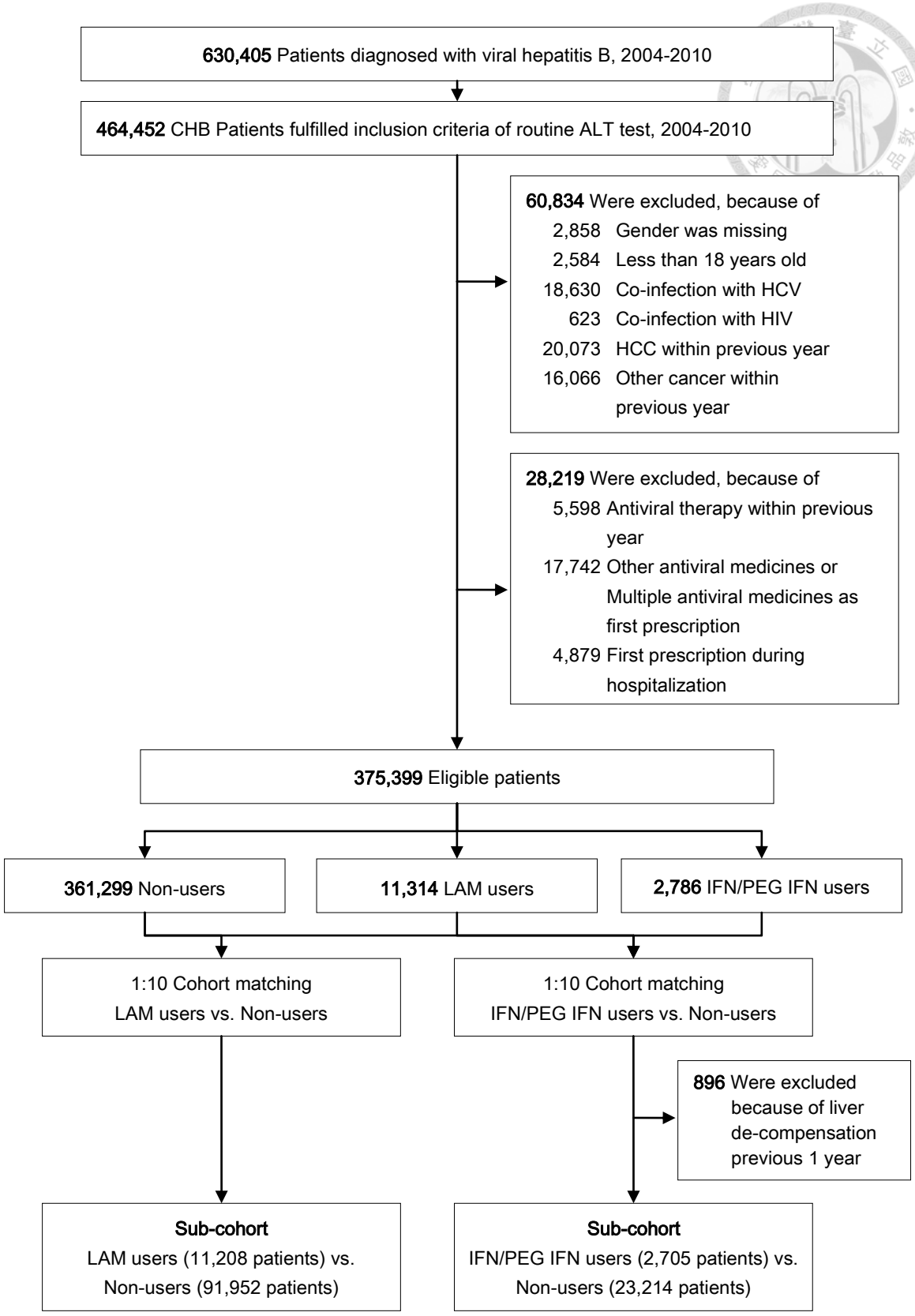


Figure 6. Flow diagram of study 1

Lamivudine vs. Untreated CHB Patients

Baseline characteristics

Table 2 presents the baseline characteristics of the sub-cohort that received lamivudine therapy and those of matched controls without antiviral treatment before and after covariates adjustment. Compared with the untreated patients, those who received lamivudine presented a higher percentage of liver cirrhosis (17.0% in LAM users vs. 7.5% in non-users), liver disease complications (including ascites [4.0% in LAM users vs. 1.6% in non-users] and esophageal varices [3.7% in LAM users vs. 1.8% in non-users]), and hospitalization (21.9% in LAM users vs. 6.7% in non-users) or emergency department visits (9.8% in LAM users vs. 2.8% in non-users) for liver disease in the past 6 months.

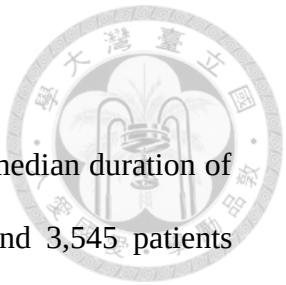
To eliminate the effect of confounders, we used propensity scores methods and employed inverse probability treatment weighting (IPTW), standardized mortality ratio weighting (SMRW) and PS matching to adjust. The Kernel density plot of propensity score is shown in the supplementary figure 1 (panel A).

Following IPTW, no differences were observed between sub-cohort of lamivudine and untreated patients, in terms of baseline characteristics. However, the difference in percentage of alcoholic liver disease was slightly increased (Before: 3.3 % in LAM user vs. 3.1% in non-user; after: 4.4% in LAM user vs. 3.1% in non-user). After SMR weighting and PS matching, we observed the similar results that no differences of baseline characteristics between two group (Table 2). The fully baseline characteristics of the sub-cohort is shown in the supplementary table 1 to 4.

Table 2. Baseline characteristics of patients treated with lamivudine compared with untreated patients

Variables	Before covariates adjustment			After IPTW			After SMRW			PS matching		
	LAM (n=11,208)	Untreated (n=91,952)	Standardized difference (%)	LAM	Untreated	Standardized difference (%)	LAM	Untreated	Standardized difference (%)	LAM (n=6,148)	Untreated (n=6,148)	Standardized difference (%)
Male sex (%)	74.0	71.9	4.7	73.2	72.2	2.4	74.0	74.3	0.8	73.2	73.2	0.0
Age (%)												
18-24	11.0	11.8	2.7	11.8	11.7	0.1	11.0	11.0	0.3	15.4	15.4	0.0
25-34	28.1	31.2	6.8	30.5	30.9	0.8	28.1	27.8	0.7	34.5	34.5	0.0
35-44	25.5	25.0	1.2	25.1	25.0	0.1	25.5	25.3	0.3	25.4	25.4	0.0
45-54	19.9	17.3	6.8	17.3	17.6	0.7	19.9	20.0	0.3	14.1	14.1	0.0
55-64	10.4	9.4	3.5	9.7	9.5	0.4	10.4	10.7	0.7	7.4	7.4	0.0
≥65	5.1	5.3	1.1	5.8	5.3	1.9	5.1	5.3	1.0	3.3	3.3	0.0
Liver disease (%)												
Alcoholic liver disease	3.3	3.1	1.8	4.4	3.1	7.2	3.3	3.5	0.9	1.0	1.3	3.5
Cirrhosis of liver without mention of alcohol	17.0	7.5	29.2	10.6	8.8	6.4	17.0	18.7	4.4	5.9	5.4	2.0
Complication of liver disease (%)												
Ascites	4.0	1.6	14.6	2.5	1.9	3.8	4.0	4.5	2.3	1.2	1.0	1.7
Hepatic encephalopathy	2.2	1.1	8.2	1.7	1.3	3.1	2.2	2.4	1.0	0.8	0.8	0.4
Esophageal varices	3.7	1.8	11.6	2.6	2.0	3.5	3.7	4.0	1.5	1.4	1.4	0.3
Hapatorenal syndrome	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	1.8
Acute liver disease previous 1 year												
Hospitalization (%)												
In the past 6 months	21.9	6.7	44.4	8.8	8.5	0.9	21.9	22.8	2.0	4.2	4.6	2.0
>6 months	3.9	2.6	7.1	2.9	2.7	1.0	3.9	3.9	0.1	1.4	1.7	2.1
Never	74.2	90.7	44.3	88.3	88.8	1.3	74.2	73.4	2.0	94.4	93.7	2.8
Emergency department visit (%)												
In the past 6 months	9.8	2.8	28.8	4.2	3.7	2.6	9.8	10.8	3.2	1.6	1.6	0.1
>6 months	1.7	1.1	5.7	1.3	1.1	1.4	1.7	1.8	0.6	0.7	0.7	0.2
Never	88.5	96.1	28.8	94.5	95.2	3.0	88.5	87.4	3.2	97.7	97.7	0.0

Variables	Before covariates adjustment			After IPTW			After SMRW			PS matching		
	LAM (n=11,208)	Untreated (n=91,952)	Standardized difference (%)	LAM	Untreated	Standardized difference (%)	LAM	Untreated	Standardized difference (%)	LAM (n=6,148)	Untreated (n=6,148)	Standardized difference (%)
Co-morbidity (%)												
Myocardial infarction	0.2	0.2	1.3	0.2	0.2	0.4	0.2	0.2	0.3	0.1	0.0	2.3
Congestive heart failure	1.1	1.1	0.0	1.4	1.1	2.6	1.1	1.2	0.8	0.5	0.5	0.7
Peripheral vascular disease	0.4	0.5	1.0	0.5	0.5	0.9	0.4	0.4	0.3	0.3	0.2	1.3
Cerebrovascular disease	1.5	1.8	2.2	2.0	1.7	1.9	1.5	1.5	0.4	0.5	0.7	2.8
Dementia	0.2	0.2	0.4	0.3	0.2	1.6	0.2	0.2	0.1	0.1	0.1	0.0
Chronic pulmonary disease	4.1	4.5	1.8	4.9	4.5	2.1	4.1	4.3	0.8	2.0	2.0	0.2
Rheumatic disease	1.2	0.9	3.2	0.9	0.9	0.5	1.2	1.2	0.1	0.3	0.3	0.0
Peptic ulcer disease	19.1	13.3	15.8	15.4	14.1	2.8	19.1	20.1	2.3	8.7	9.0	1.1
Diabetes	8.8	8.9	0.2	9.6	8.9	2.6	8.8	9.1	1.2	4.1	4.2	0.5
Hemiplegia or paraplegia	0.2	0.2	0.5	0.3	0.2	0.5	0.2	0.2	0.0	0.1	0.1	2.0
Renal disease	2.2	1.4	5.6	2.0	1.5	3.5	2.2	2.4	1.7	1.5	1.0	5.1
Calendar year												
2004	23.6	21.7	4.5	23.4	22.0	3.4	23.6	24.3	1.8	24.4	24.4	0.0
2005	22.0	20.9	2.7	21.6	21.1	1.2	22.0	22.2	0.4	22.6	22.6	0.0
2006	18.3	17.9	0.8	17.6	18.0	0.8	18.3	18.1	0.4	17.8	17.8	0.0
2007	18.4	19.3	2.2	18.6	19.1	1.5	18.4	18.2	0.7	18.1	18.1	0.0
2008	10.4	11.5	3.3	11.0	11.3	1.1	10.4	10.2	0.8	10.4	10.4	0.0
2009	2.9	3.4	2.9	3.0	3.3	1.5	2.9	2.8	0.5	2.9	2.9	0.0
2010	4.4	5.3	4.2	4.8	5.2	1.9	4.4	4.2	0.8	3.9	3.9	0.0



HCC incidence, liver-related mortality and all cause mortality

In this sub-cohort, lamivudine treatment was administered for a median duration of 16.6 months (inter-quartile range [IQR]: 10.8 to 18.0 months) and 3,545 patients (31.6%) with lamivudine were added or switched to other anti-HBV agents during follow-up period. All patients were followed up for a median of 50.3 months (IQR: 33.5 to 67.9 months), with the exception of the 6,544 (6.3%) patients who developed HCC, the 8,258 (8.0%) patients who died, and 5,143 (5.0%) patients who were death due to liver-related disease (Supplementary table 1 to 4).

Figure 7 to 9 and Table 3 present the cumulative incidence curves and hazard ratios for the incidence of HCC, death from liver-related causes, and all-cause mortality within this sub-cohort. The crude incidence rate for HCC was lower among lamivudine treated patients, compared with untreated patients (first-exposure-carried-forward: hazard ratio [HR], 0.69; 95%CI, 0.63-0.76; as-treated: HR, 0.61; 95%CI, 0.55-0.67). However, the reduction in liver-related mortality (lamivudine compared with non-users, first-exposure-carried-forward: HR, 1.12; 95%CI, 1.03 -1.33; as-treated: HR, 1.02; 95%CI, 0.93-1.12) and all-cause mortality (lamivudine compared with non-users, first-exposure-carried-forward: HR, 1.04; 95%CI, 0.97 -1.11; as-treated: HR, 0.97; 95%CI, 0.90-1.04) were comparable between the two groups (Figure 7, Table 3).

After IPTW, in primary analysis (first-exposure-carried-forward) as well as in secondary analysis (as-treated), the lamivudine treated patients presented a lower risk of HCC incidence (first-exposure-carried-forward: HR, 0.54; 95%CI, 0.48-0.59; as-treated: HR, 0.46; 95%CI, 0.41-0.51), liver-related mortality (first-exposure-carried-forward: HR, 0.77; 95%CI, 0.70-0.85; as-treated: HR, 0.68;

95%CI, 0.61-0.77), and all-cause mortality (first-exposure-carried-forward: HR, 0.76; 95%CI, 0.70-0.83; as-treated: HR, 0.70; 95%CI, 0.64-0.76), compared to the untreated group (Figure 8, Table 3).

We tried to adjust informative censoring by using inverse probability of censoring weighting (IPCW). We observed that the lamivudine treated patients presented a similar risk of HCC incidence (HR, 1.04; 95%CI, 0.94-1.14), liver-related mortality (HR, 1.03; 95%CI, 0.94-1.13), and all-cause mortality (HR, 0.98; 95%CI, 0.92-1.06), compared to the untreated group (Figure 9 [panel E], Table 3). Furthermore, the final analyses incorporated inverse probability of treatment weighting (IPTW) and inverse probability of censoring weighting (IPCW). Compared with untreated patients, a decrease in HCC incidence (HR, 0.78; 95%CI, 0.70-0.88), liver-related mortality (HR, 0.69; 95%CI, 0.62-0.78), and all-cause mortality (HR, 0.71; 95%CI, 0.65-0.78) was observed among lamivudine treated patients (Figure 9 [panel F], Table 3).

We also estimated the effectiveness of lamivudine treatments in mitigating the incidence of HCC and mortality among patients who differed in terms of sex, age, alcoholic liver disease, cirrhosis, diabetes and renal disease. The effects of lamivudine did not differ in all subgroups. Among chronic hepatitis patients without evidence of liver decompensation, the use of lamivudine was still significantly associated with a decrease in the risk of HCC, liver-related mortality, and all-cause mortality, compared with patients who did not use anti-HBV agents (Figure 8).

In addition, we tried to use different analyses to deal with potential confounding factor and observed similar results in this group (Table 4).

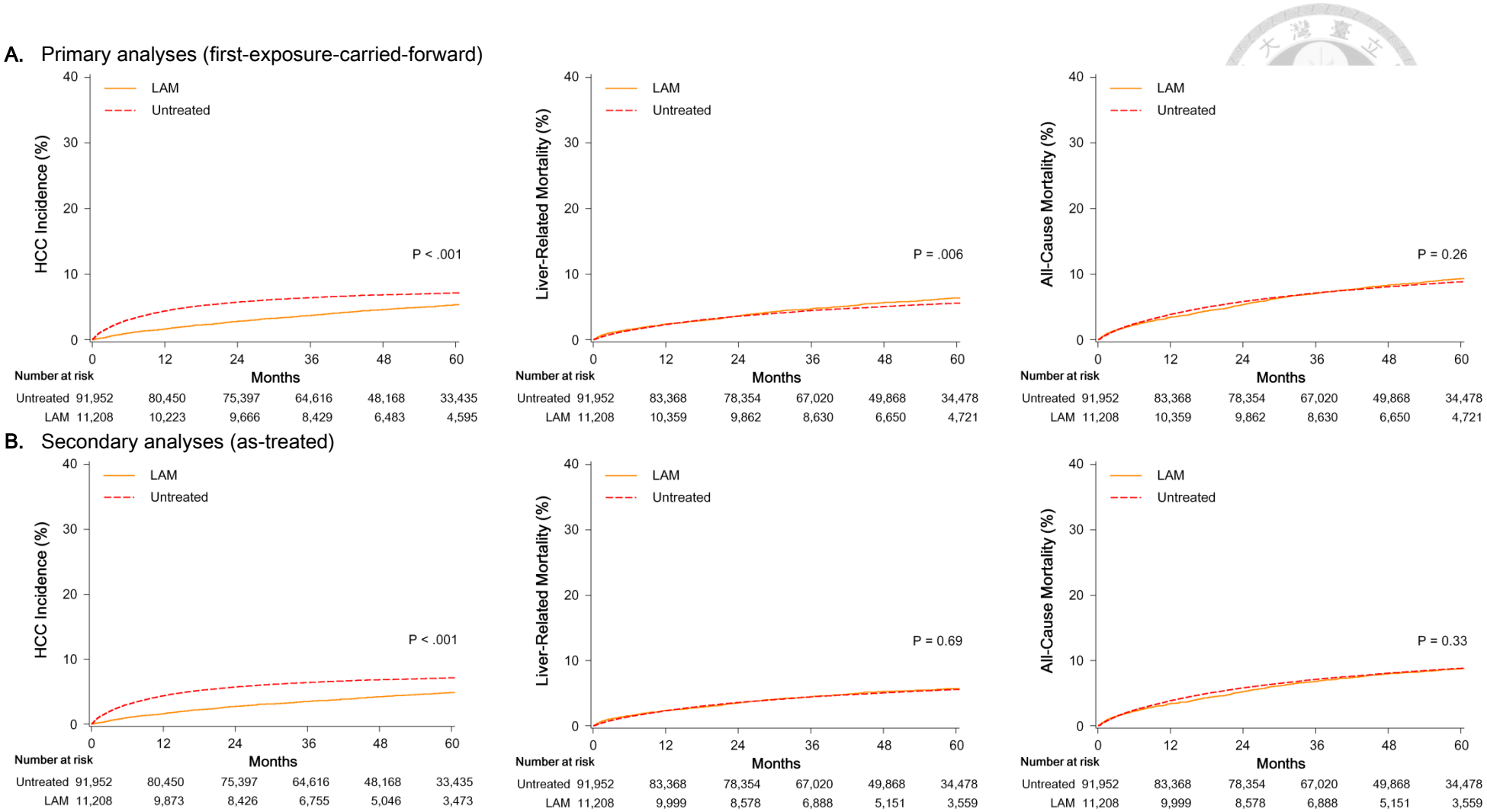
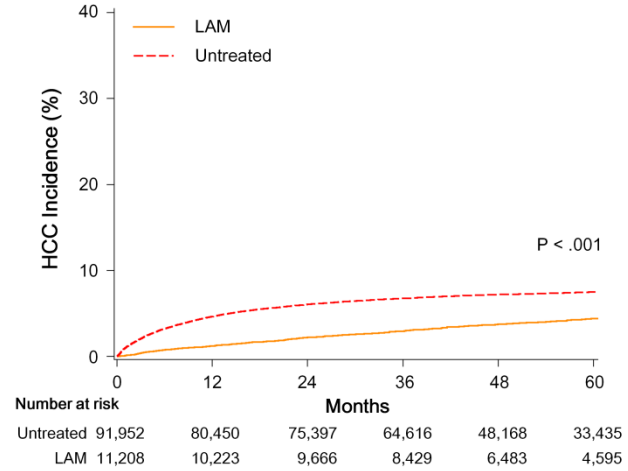
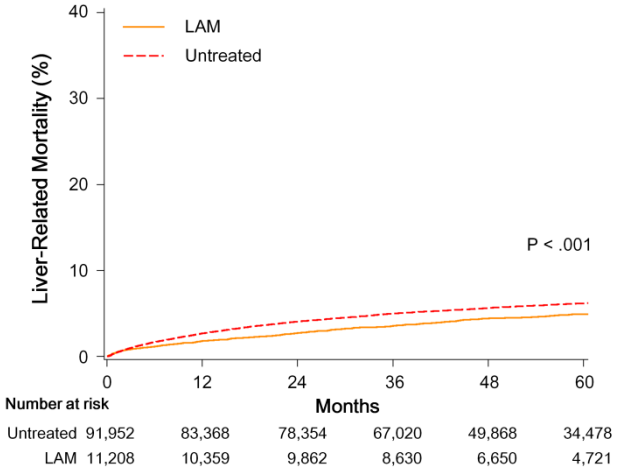


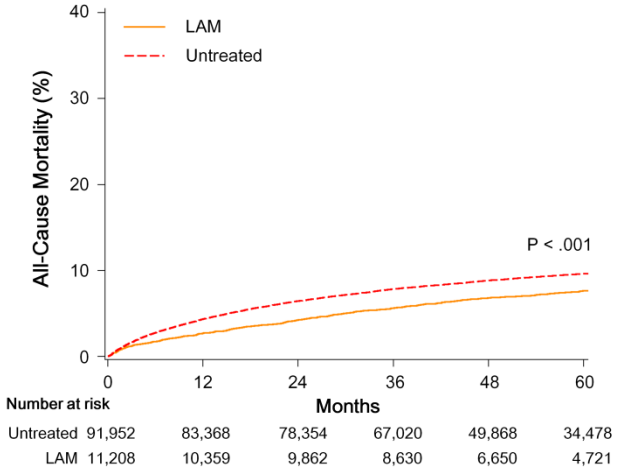
Figure 7. Cumulative incidence curves for HCC, liver-related death, and death from all cause associated with lamivudine use-1

A and B: These analyses were crude cumulative incidence curve.

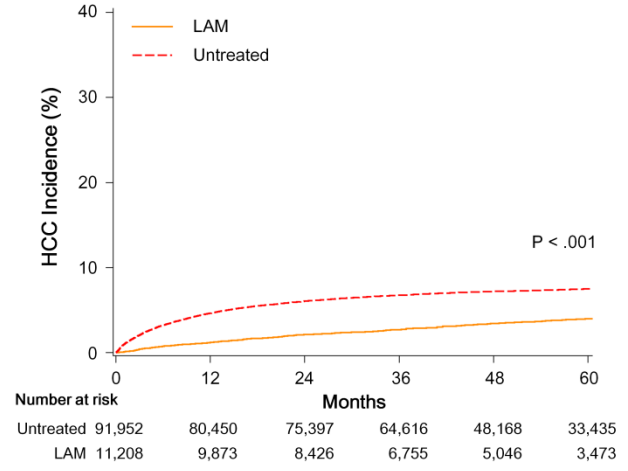
C. Primary analyses (first-exposure-carried-forward)

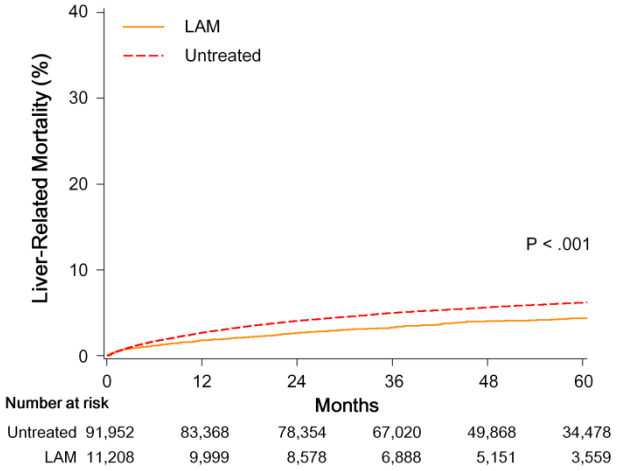






D. Secondary analyses (as-treated)





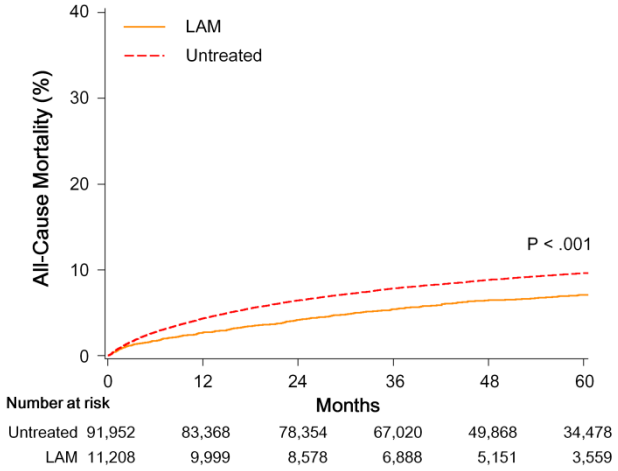


Figure 8. Cumulative incidence curves for HCC, liver-related death, and death from all cause associated with lamivudine use-2

C and D: These analyses were employed inverse probability treatment weighting (IPTW).

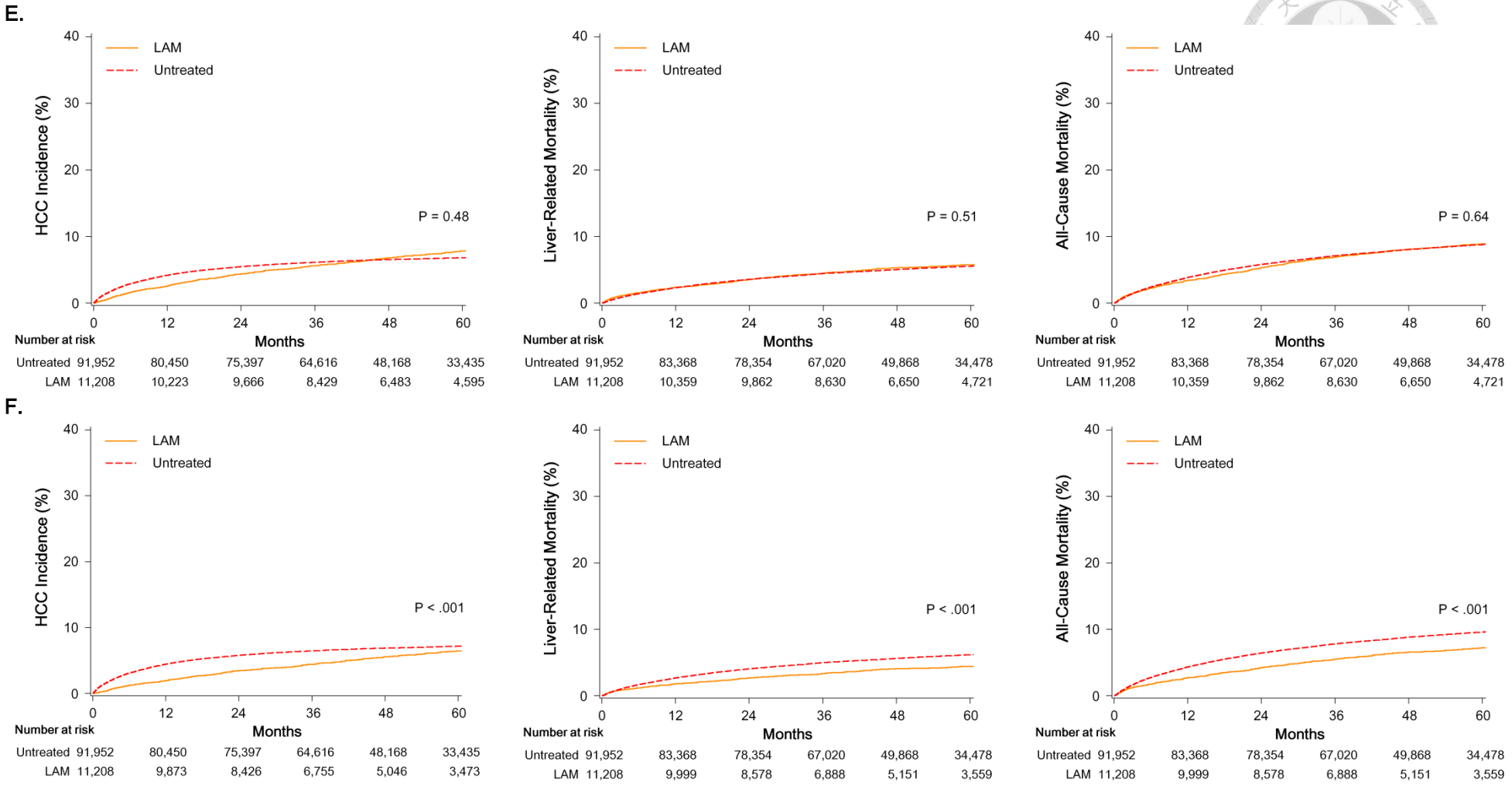


Figure 9. Cumulative incidence curves for HCC, liver-related death, and death from all cause associated with lamivudine use-3

E: These analyses were employed inverse probability of censoring weighting (IPCW). F: These analyses were employed IPCW and IPTW.

Table 3. Hazard ratios for HCC incidence, liver-related mortality, and all causes mortality associated with lamivudine use

Type of analysis and outcome	LAM (N=11,208)	Untreated* (n=91,952)	Crude Hazard ratio(95%CI)	Adjusted Hazard Ratio(95%CI) †
Primary analysis				
(first-exposure-carried-forward analysis)				
HCC incidence				
No. of event	527	6,017	0.69	0.54
No. /1000 person-year	11.1	16.5	(0.63 to 0.76)	(0.48 to 0.59)
Liver-related mortality				
No. of event	637	4,506	1.12	0.77
No. /1000 person-yr	13.1	11.9	(1.03 to 1.22)	(0.70 to 0.85)
All-cause mortality				
No. of event	954	7,304	1.04	0.76
No. /1000 person-yr	19.7	19.3	(0.97 to 1.11)	(0.70 to 0.83)
Secondary analysis				
(as-treated analysis)				
HCC incidence				
No. of event	434	6,017	0.61	0.46
No. /1000 person-yr	10.6	16.5	(0.55 to 0.67)	(0.41 to 0.51)
Liver-related mortality				
No. of event	526	4,506	1.02	0.68
No. /1000 person-yr	12.6	11.9	(0.93 to 1.12)	(0.61 to 0.77)
All-cause mortality				
No. of event	809	7,304	0.97	0.70
No. /1000 person-yr	19.4	19.3	(0.90 to 1.04)	(0.64 to 0.76)
Inverse probability censoring weighting				
HCC incidence			1.04 (0.94 to 1.14)	0.78 (0.70 to 0.88)
Liver-related mortality			1.03 (0.94 to 1.13)	0.69 (0.62 to 0.78)
All-cause mortality			0.98 (0.92 to 1.06)	0.71 (0.65 to 0.78)

*Reference group.

†These analyses employed inverse probability treatment weighting (IPTW).

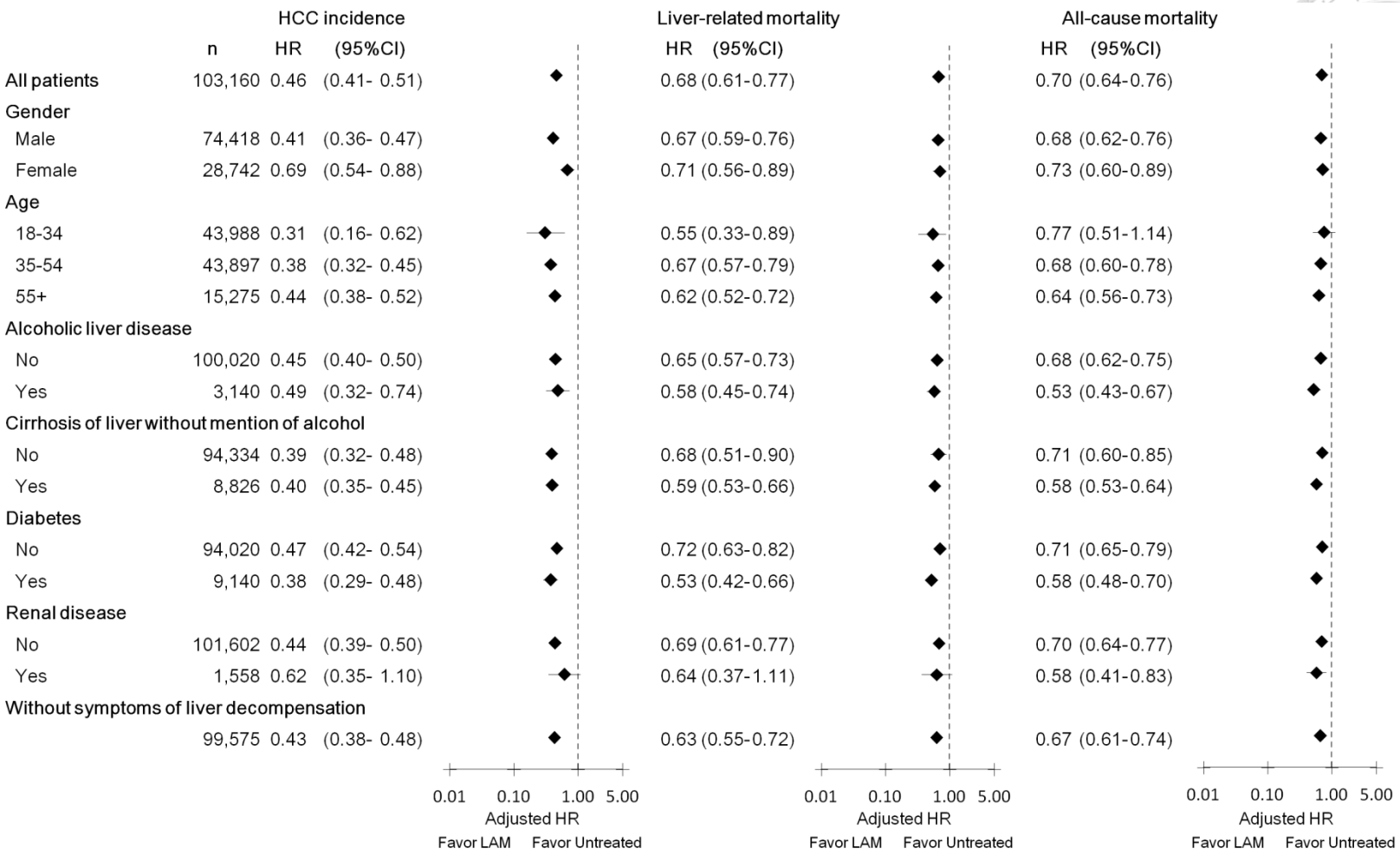


Figure 10. Subgroup analyses of HCC incidence, liver-related mortality, and all causes mortality for patients treated with lamivudine versus those who were not given anti-HBV treatment.

These analyses were using secondary analysis (as-treated analysis) and employed inverse probability treatment weighting (IPTW).

Table 4. Sensitivity analyses for HCC incidence, liver-related mortality, and all causes mortality associated with lamivudine use

		LAM vs. Untreated(ref.)	
Type of covariates adjustment / Outcome	n	Hazard ratio*	(95%CI)
Inverse probability treatment weighting	103,160		
HCC incidence		0.46	(0.41 to 0.51)
Liver-related mortality		0.68	(0.61 to 0.77)
All-cause mortality		0.70	(0.64 to 0.76)
Standardized mortality ratio weighting	103,160		
HCC incidence		0.40	(0.36 to 0.44)
Liver-related mortality		0.48	(0.43 to 0.52)
All-cause mortality		0.50	(0.46 to 0.54)
Propensity score matching	12,296		
HCC incidence		0.26	(0.22 to 0.32)
Liver-related mortality		0.43	(0.35 to 0.52)
All-cause mortality		0.44	(0.38 to 0.51)
Multivariable adjusting	103,160		
HCC incidence		0.34	(0.31 to 0.37)
Liver-related mortality		0.51	(0.46 to 0.56)
All-cause mortality		0.52	(0.49 to 0.57)

*These analyses were using secondary analysis (as-treated analysis)

Interferon or Peg-interferon vs. Untreated CHB Patients

Baseline characteristics

Compared to patients who did not receive anti-HBV agents, those administered interferon or peg-interferon presented a lower percentage of alcoholic liver disease (0.6% in IFN/PEG-IFN users vs. 2.2% in non-users), but a higher percentage of hospitalization for liver disease in the past 6 months (13.6% in IFN/PEG-IFN users vs. 3.9% in non-users) (Table 5). We also used propensity scores methods and employed inverse probability treatment weighting (IPTW), standardized mortality ratio weighting (SMRW) and PS matching to minimize the effect of confounding factors. The Kernel density plot of propensity score is shown in the supplementary figure 1 (panel B).

Following IPTW, no differences were observed in baseline characteristics between these two matched groups, except alcoholic liver disease (4.7% in IFN/PEG-IFN users vs. 2.0% in non-users). After SMR weighting and PS matching, we observed the similar results that no differences of baseline characteristics between two group (Table 2). The imbalanced covariates will further adjust in final models. The fully baseline characteristics of the sub-cohort is shown in the supplementary table 5 to 8.

Table 5. Baseline characteristics of patients treated with interferon or peg-interferon compared with untreated patients

Variables	Before covariates adjustment			After IPTW			After SMRW			PS matching		
	IFN (n=2,705)	Untreated (n=23,214)	Standardized difference (%)	IFN	Untreated	Standardized difference (%)	IFN	Untreated	Standardized difference (%)	IFN (n=1,884)	Untreated (n=1,884)	Standardized difference (%)
Male sex (%)	77.2	74.9	5.5	75.8	75.1	1.6	77.2	77.4	0.4	75.7	75.7	0.0
Age (%)												
18-24	12.0	13.3	3.9	12.4	13.1	2.0	12.0	11.9	0.3	13.5	13.5	0.0
25-34	36.4	37.7	2.7	38.3	37.6	1.4	36.4	36.5	0.2	38.8	38.8	0.0
35-44	29.1	27.0	4.7	26.1	27.2	2.6	29.1	29.1	0.0	27.3	27.3	0.0
45-54	17.0	16.3	1.8	17.5	16.4	3.1	17.0	16.9	0.1	15.8	15.8	0.0
55-64	4.9	5.1	0.8	5.0	5.0	0.2	4.9	4.9	0.0	3.9	3.9	0.0
≥65	0.6	0.7	0.9	0.7	0.7	0.3	0.6	0.7	0.5	0.7	0.7	0.0
Liver disease (%)												
Alcoholic liver disease	0.6	2.2	14.0	4.7	2.0	15.1	0.6	0.6	0.2	<0.1*	0.0	3.3
Cirrhosis of liver without mention of alcohol	4.7	4.2	2.2	4.7	4.3	1.8	4.7	5.0	1.6	2.1	2.2	0.7
Acute liver disease previous 1 year												
Hospitalization (%)												
In the past 6 months	13.6	3.9	35.1	4.1	4.9	3.6	13.6	13.4	0.7	1.4	1.5	0.9
>6 months	2.8	2.2	4.2	2.1	2.3	1.0	2.8	2.9	0.1	0.4	0.6	3.1
Never	83.5	93.9	33.4	93.8	92.9	3.6	83.5	83.7	0.6	98.2	97.9	2.3
Emergency department visit (%)												
In the past 6 months	1.9	1.4	3.5	1.6	1.5	0.7	1.9	2.0	1.0	0.3	0.3	1.0
>6 months	0.9	0.7	1.9	0.8	0.7	1.3	0.9	1.0	1.1	0.3	0.3	0.0
Never	97.3	97.9	4.0	97.6	97.8	1.3	97.3	97.0	1.4	99.4	99.4	0.7
Co-morbidity (%)												
Myocardial infarction	0.2	0.1	0.5	0.2	0.1	0.6	0.2	0.2	0.1	0.0	0.0	0.0
Congestive heart failure	0.2	0.5	5.0	0.6	0.5	1.1	0.2	0.2	0.2	<0.1*	<0.1*	1.9
Peripheral vascular disease	0.2	0.3	1.8	0.3	0.3	0.3	0.2	0.2	0.3	<0.1*	0.0	3.3
Cerebrovascular	0.7	1.0	3.2	1.5	0.9	5.3	0.7	0.7	0.5	0.4	0.3	1.9

Variables	Before covariates adjustment			After IPTW			After SMRW			PS matching		
	IFN (n=2,705)	Untreated (n=23,214)	Standardized difference (%)	IFN	Untreated	Standardized difference (%)	IFN	Untreated	Standardized difference (%)	IFN (n=1,884)	Untreated (n=1,884)	Standardized difference (%)
disease												
Dementia	0.0	0.0	3.1	0.0	0.0	2.9	0.0	0.0	0.0	0.0	0.0	0.0
Chronic pulmonary disease	2.9	3.3	2.7	3.4	3.3	0.5	2.9	3.0	0.6	1.8	1.1	5.8
Rheumatic disease	0.6	0.6	0.2	0.6	0.6	0.5	0.6	0.6	0.0	0.2	0.3	1.1
Peptic ulcer disease	12.2	9.5	8.8	10.5	9.8	2.4	12.2	12.8	1.7	6.3	5.3	4.1
Diabetes	6.2	7.1	3.8	8.5	7.1	5.6	6.2	6.5	1.2	3.3	3.6	1.5
Hemiplegia or paraplegia	0.0	0.2	4.5	0.2	0.2	0.4	0.0	0.0	0.0	0.0	0.0	0.0
Renal disease	0.9	1.0	1.3	1.1	1.0	1.4	0.9	0.9	0.6	0.2	0.3	3.3
Calendar year												
2004	4.0	2.8	6.7	2.9	3.0	0.3	4.0	4.2	0.8	3.6	3.6	0.0
2005	6.8	5.5	5.4	5.2	5.7	2.2	6.8	6.6	0.8	5.9	5.9	0.0
2006	19.3	17.5	4.6	16.9	17.7	2.0	19.3	19.1	0.4	17.6	17.6	0.0
2007	16.3	16.0	0.8	15.3	16.0	2.0	16.3	16.3	0.1	16.4	16.4	0.0
2008	18.1	18.6	1.2	17.7	18.5	2.2	18.1	17.9	0.6	17.7	17.7	0.0
2009	18.4	20.3	4.9	20.6	20.1	1.2	18.4	18.3	0.1	19.2	19.2	0.0
2010	17.1	19.3	5.7	21.5	19.1	6.0	17.1	17.5	1.1	19.6	19.6	0.0

*The exact number of patients below 3 are not specified, in accordance with Taiwan privacy regulations

HCC incidence, liver-related mortality and all cause mortality

In the sub-cohort of interferon or peg-interferon versus matched untreated patients, the median duration of the treatment period was 5.6 months (IQR: 5.0 to 9.4 months), with 184 (6.8%) patients receiving interferon and 2,521 (93.2%) patients receiving peg-interferon and 460 patients (17.0%) with interferon or peg-interferon were added or switched to other anti-HBV agents during follow-up period. All patients were followed up for a median of 27.7 months (IQR: 13.1 to 45.9 months), with the exception of the 1,354 (5.2%) patients who developed HCC, the 1,262 (4.9%) patients who died and 661 (2.5%) patients who were death due to liver-related disease (Supplementary table 5 to 8).

The crude incidence rate for HCC (first-exposure-carried-forward: hazard ratio [HR], 0.26; 95%CI, 0.19-0.35; as-treated: HR, 0.24; 95%CI, 0.18-0.33), liver-related mortality (first-exposure-carried-forward: HR, 0.17; 95%CI, 0.10 -0.29; as-treated: HR, 0.12; 95%CI, 0.07-0.23) and all-cause mortality (first-exposure-carried-forward: HR, 0.13; 95%CI, 0.08 -0.20; as-treated: HR, 0.10; 95%CI, 0.06-0.16) was lower among interferon or peg-interferon treated patients, compared with untreated patients (Figure 11, Table 6).

Compared with untreated patients, a clear decrease in HCC incidence (first-exposure-carried-forward: HR, 0.23; 95%CI, 0.17-0.33; as-treated: HR, 0.22; 95%CI, 0.15-0.31), liver-related mortality (first-exposure-carried-forward: HR, 0.18; 95%CI, 0.10-0.32; as-treated: HR, 0.14; 95%CI, 0.07-0.27), and all-cause mortality (first-exposure-carried-forward: HR, 0.12; 95%CI, 0.07-0.20; as-treated: HR, 0.10; 95%CI, 0.06-0.18) was observed among interferon treated patients, after inverse probability of treatment weighting (Figure 12, Table 6).

Figure 9 and table 3 present the cumulative incidence curves and hazard ratios for the incidence of HCC, death from liver-related causes, and all-cause mortality within the sub-cohort of interferon or peg-interferon treated patients and untreated patients after inverse probability of censoring weighting (IPCW) as well as inverse probability of treatment weighting (IPTW) incorporated inverse probability of censoring weighting (IPCW) . After IPCW, we observed that the interferon or peg-interferon treated patients presented a similar risk of HCC incidence (HR, 0.95; 95%CI, 0.70-1.29); however, a lower risk of liver-related mortality (HR, 0.54; 95%CI, 0.26-1.11), all-cause mortality (HR, 0.37; 95%CI, 0.19-0.74), compared to the untreated group (Figure 13 [panel E], Table 6). Incorporating IPTW and IPCW, a decrease in HCC incidence (HR, 0.85; 95%CI, 0.61-1.20), liver-related mortality (HR, 0.57; 95%CI, 0.25-1.32), and all-cause mortality (HR, 0.34; 95%CI, 0.16-0.72) was observed among interferon or peg-interferon treated patients, compared with untreated patients (Figure 13 [panel F], Table 6).

We also estimated the effectiveness of interferon or peg-interferon treatments in mitigating the incidence of HCC and mortality among patients who differed in terms of sex, age, alcoholic liver disease, cirrhosis, diabetes, and renal disease. The effectiveness of interferon or peg-interferon treatment did not differ in any of the subgroups, compared with untreated patients (Figure 14). This study employed various forms of analysis to deal with potential confounding factors and observe similar results in both groups (Table 7).

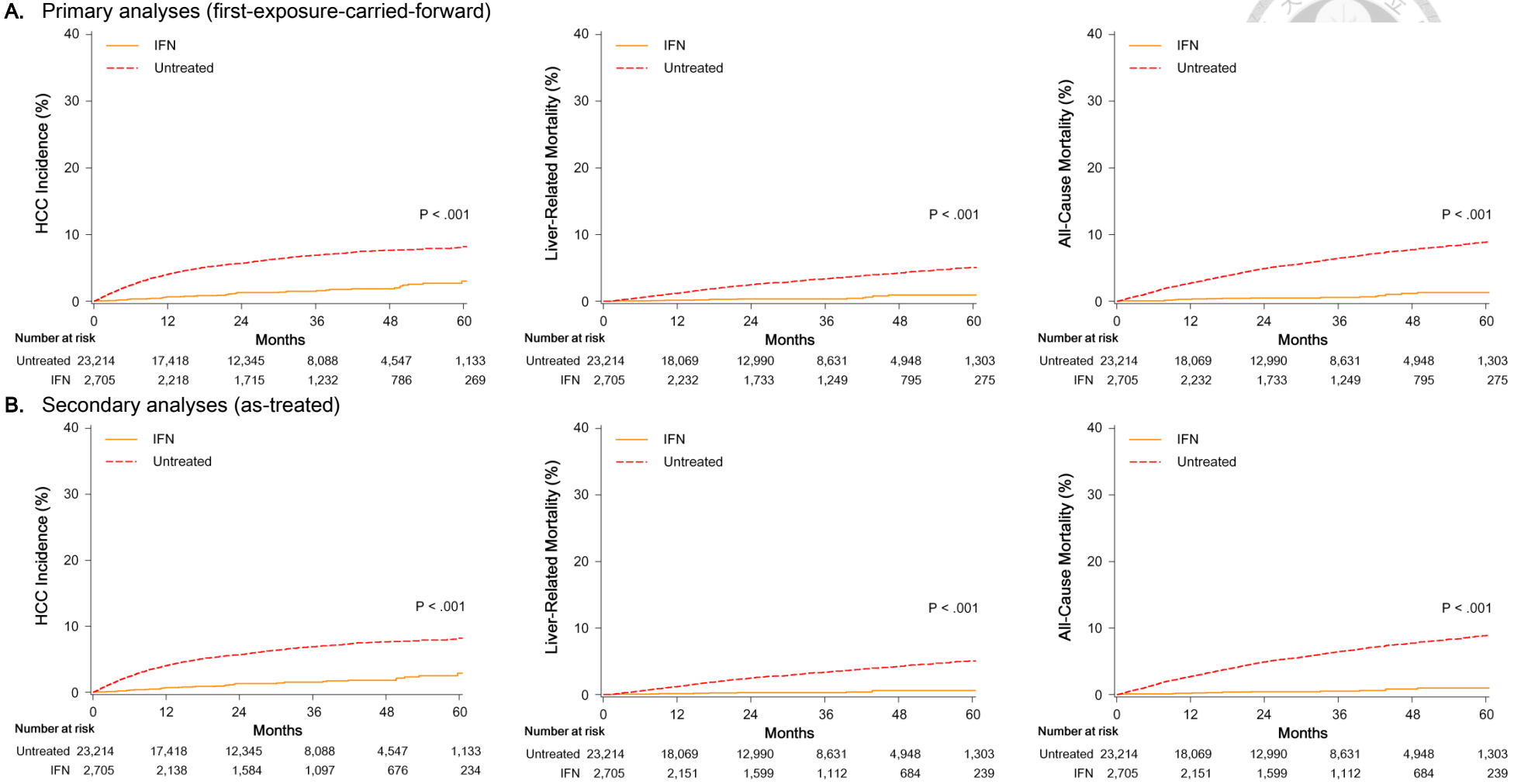


Figure 11. Cumulative incidence curves of HCC, liver-related death, and death from all cause associated with interferon use-1

A and B: These analyses were crude cumulative incidence curve.

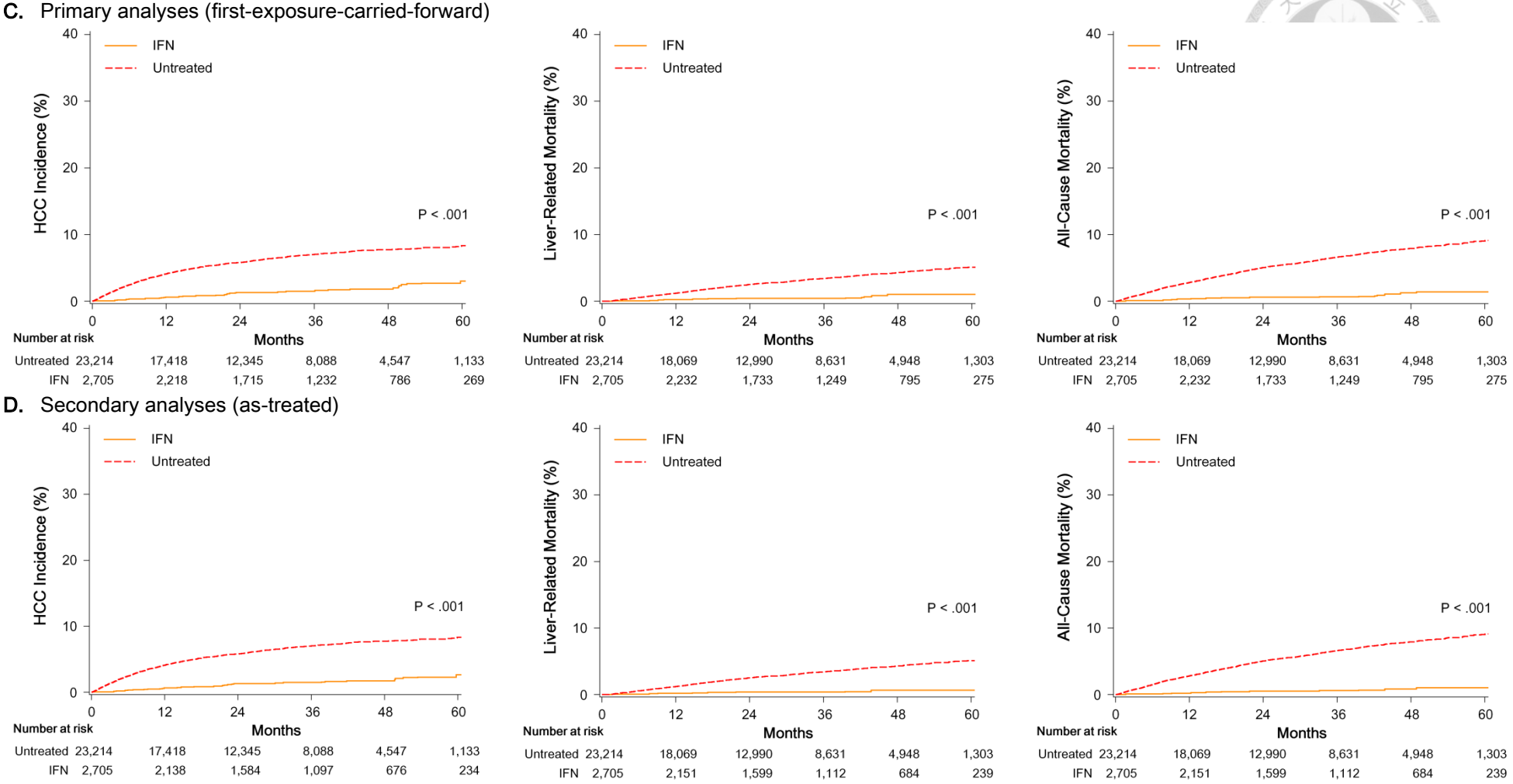


Figure 12. Cumulative incidence curves of HCC, liver-related death, and death from all cause associated with interferon use-2

C and D: These analyses were employed inverse probability treatment weighting (IPTW).

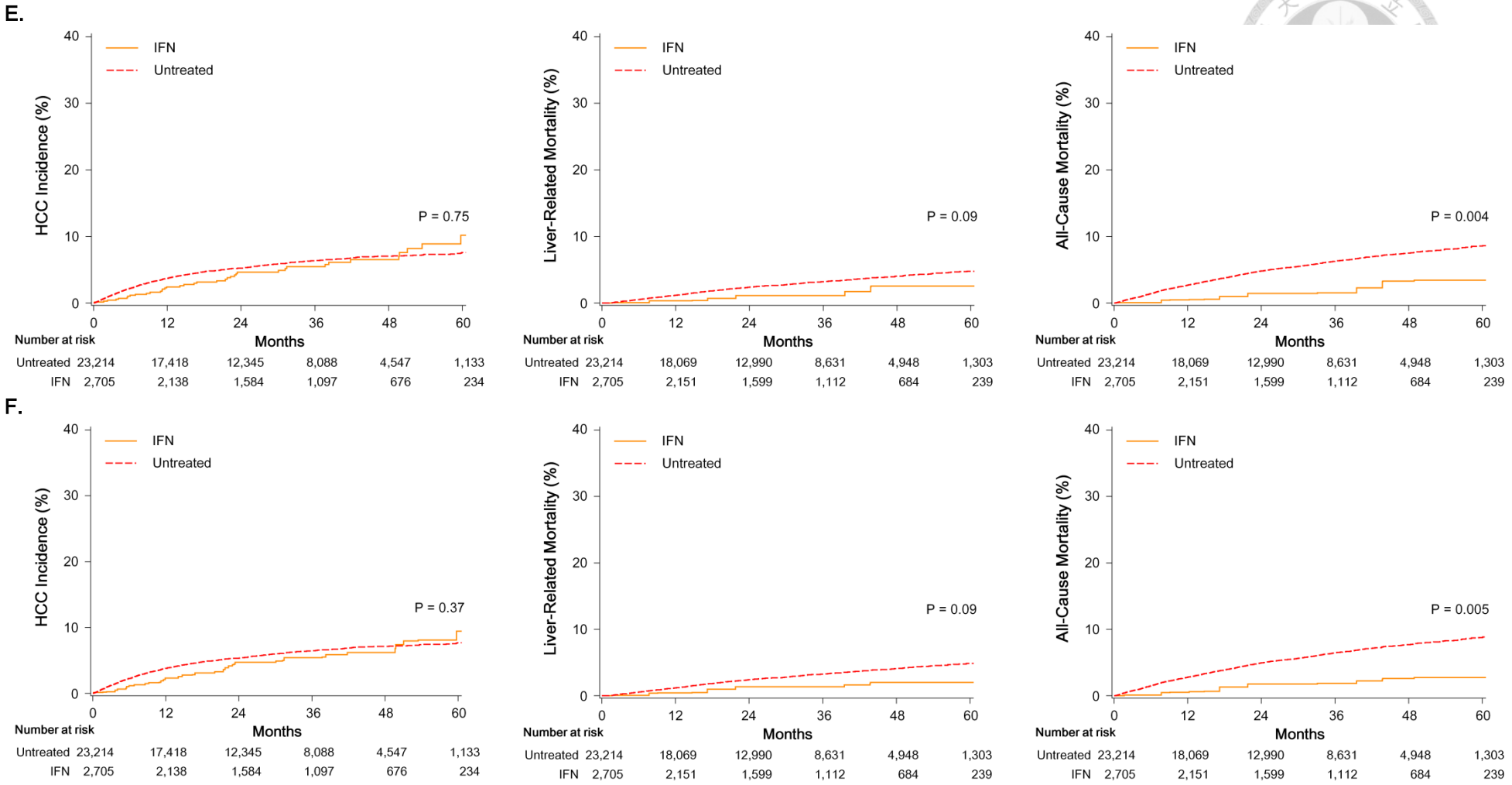


Figure 13. Cumulative incidence curves of HCC, liver-related death, and death from all cause associated with interferon use-3

E: These analyses were employed inverse probability of censoring weighting (IPCW). F: These analyses were employed IPCW and IPTW.

Table 6. Hazard ratios of HCC incidence, liver-related mortality, and all causes mortality associated with interferon use

Type of analysis and outcome	IFN/ PEG-IFN (N=2,705)	Untreated* (n=23,214)	Crude Hazard ratio(95%CI)	Adjusted Hazard Ratio(95%CI) †
Primary analysis (first-exposure-carried-forward analysis)				
HCC incidence				
No. of event	44	1,310	0.26	0.23
No. /1000 person-year	5.8	23.8	(0.19 to 0.35)	(0.17 to 0.33)
Liver-related mortality				
No. of event	15	646	0.17	0.18
No. /1000 person-yr	1.9	11.2	(0.10 to 0.29)	(0.10 to 0.32)
All-cause mortality				
No. of event	21	1,241	0.13	0.12
No. /1000 person-yr	2.7	21.6	(0.08 to 0.20)	(0.07 to 0.20)
Secondary analysis (as-treated analysis)				
HCC incidence				
No. of event	39	1,310	0.24	0.22
No. /1000 person-yr	5.5	23.8	(0.18 to 0.33)	(0.15 to 0.31)
Liver-related mortality				
No. of event	10	646	0.12	0.14
No. /1000 person-yr	1.4	11.2	(0.07 to 0.23)	(0.07 to 0.27)
All-cause mortality				
No. of event	15	1,241	0.10	0.10
No. /1000 person-yr	2.1	21.6	(0.06 to 0.16)	(0.06 to 0.18)
Inverse probability censoring weighting				
HCC incidence			0.95 (0.70 to 1.29)	0.85 (0.61 to 1.20)
Liver-related mortality			0.54 (0.26 to 1.11)	0.57 (0.25 to 1.32)
All-cause mortality			0.37 (0.19 to 0.74)	0.34 (0.16 to 0.72)

*Reference group.

†This analysis involved inverse probability treatment weighting (IPTW) with adjustments for alcoholic liver disease due to unbalance between study groups.

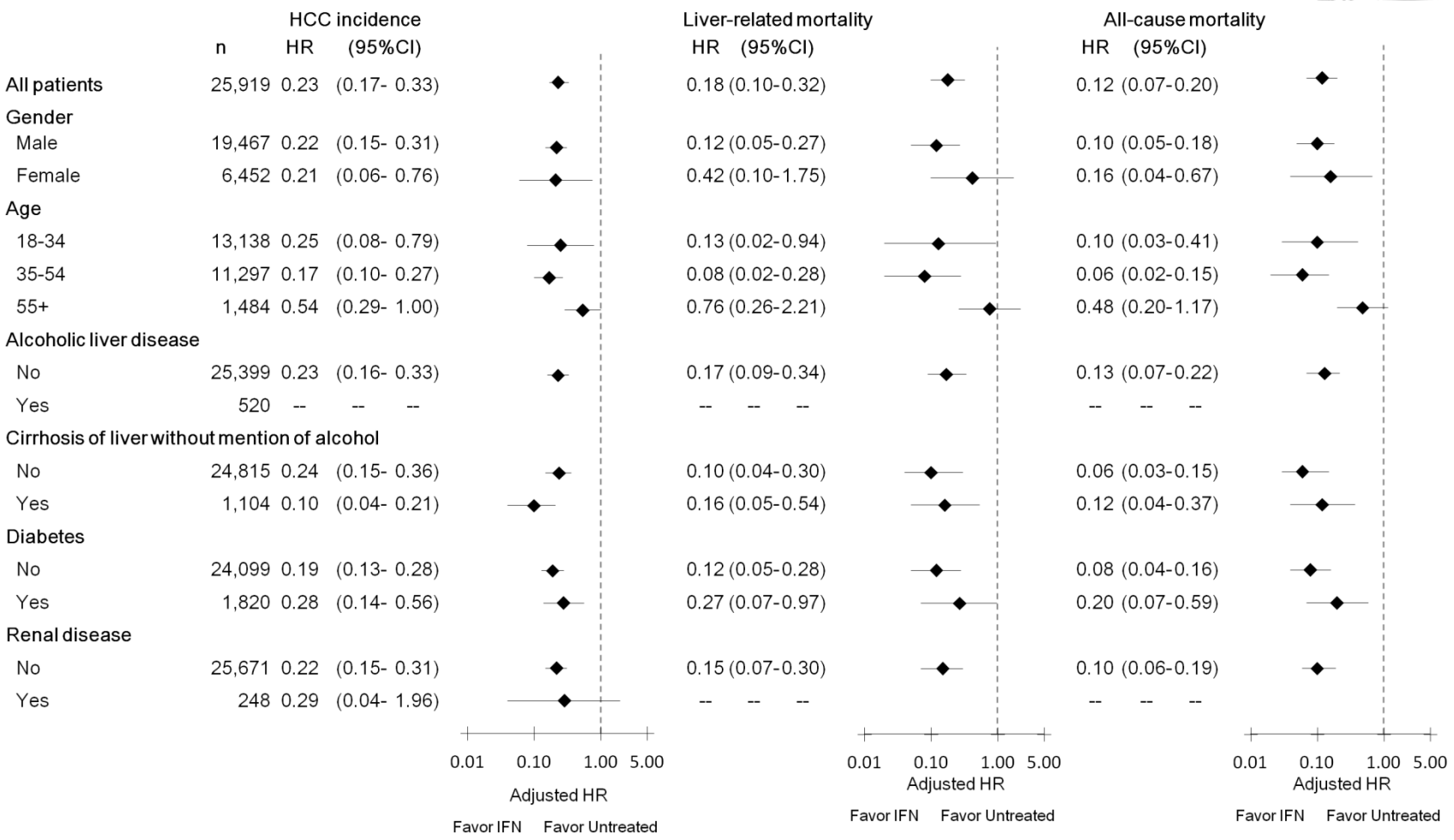


Figure 14. Subgroup analyses of HCC incidence, liver-related mortality, and all-cause mortality for patients treated with interferon or peg-interferon versus those who were not administered anti-HBV treatment.

These analyses were using secondary analysis (as-treated analysis) and employed inverse probability treatment weighting (IPTW).

Table 7. Sensitivity analyses for HCC incidence, liver-related mortality, and all causes mortality associated with interferon use

		IFN vs. Untreated(ref.)	
Type of covariates adjustment / Outcome	n	Hazard ratio*	(95%CI)
Inverse probability treatment weighting	25,919		
HCC incidence		0.23	(0.17 to 0.33) †
Liver-related mortality		0.18	(0.10 to 0.32) †
All-cause mortality		0.12	(0.07 to 0.20) †
Standardized mortality ratio weighting	25,919		
HCC incidence		0.21	(0.15 to 0.28)
Liver-related mortality		0.11	(0.06 to 0.21)
All-cause mortality		0.08	(0.05 to 0.13)
Propensity score matching	3,768		
HCC incidence		0.12	(0.08 to 0.18)
Liver-related mortality		0.10	(0.04 to 0.23)
All-cause mortality		0.07	(0.04 to 0.15)
Multivariable adjusting	25,919		
HCC incidence		0.18	(0.13 to 0.24)
Liver-related mortality		0.11	(0.06 to 0.21)
All-cause mortality		0.08	(0.05 to 0.13)

*Secondary analysis (as-treated analysis)

†This analysis employed inverse probability treatment weighting (IPTW) with adjustment for alcoholic liver disease due to unbalance between study groups.

5.2 Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment

Cohort Selection

Between January 1, 2004 and December 31, 2010, a total of 54,911 patients with newly diagnosed liver cancer were reported in the Long-Form database of the Taiwan Cancer Registry (LF-TCR). We excluded 2,985 patients who had multiple primary cancer; 117 patients who were less than 18 years old; 31,134 patients who were not diagnosed with HBV or were co-infected with HBV and HCV; 15,221 patients who did not undergo liver resection, RFA or PEI mono-therapy as the first course of HCC treatment; 495 patients who have received antiviral therapy before cancer treatment. To ensure enrolled patients who received curative therapy, we also excluded 240 patients who had an unclear surgical margin (including 175 cases who had an unclear margin and 65 cases who had missing information of surgical margin) and 381 patients who suffered from a tumor that had directly invaded adjacent organs or lymph nodes, or had undergone distant metastasis (Figure 15).

Among them, 4,578 HBV-related HCC patients were selected for analysis, including 3,831(83.7%) untreated patients and 747(16.3%) treated patients.

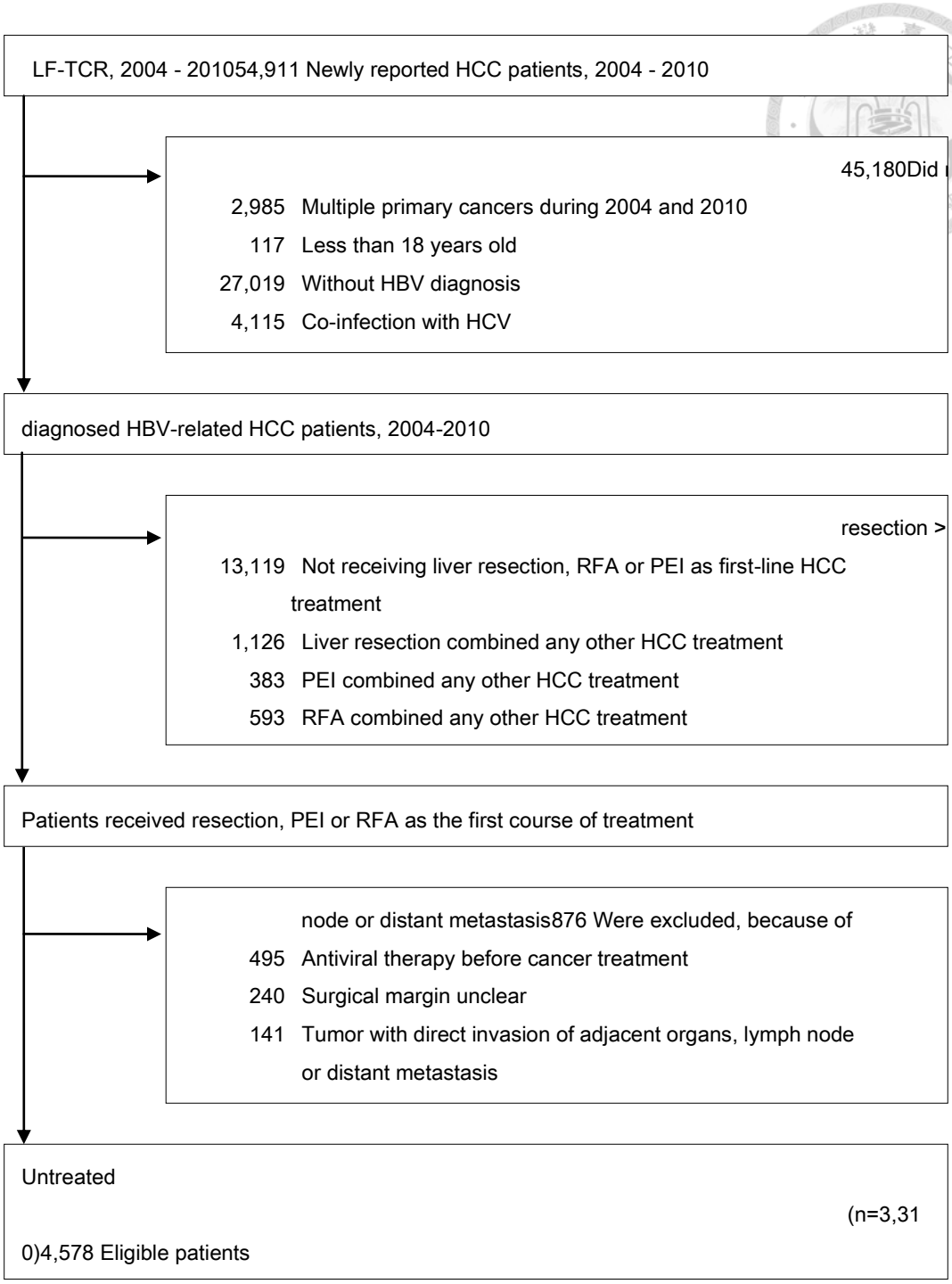


Figure 15. Flow diagram of study 2

Antiviral therapy

In this cohort, 747 (16.9%) patients received adjuvant antiviral therapy. This treatment was initiated at a median of 10.2 months (inter-quartile range [IQR]: 3.3 to 24.6 months) following the first course of HCC therapy. Among treated patients, 489 (65.5%) received entecavir monotherapy, 161 (21.6%) received lamivudine monotherapy, 67 (9.0%) received telbivudine monotherapy, and 30 (4.0%) received other medication. The median duration of antiviral therapy was 16.3 months (IQR: 9.6 to 23.5 months) (Table 8).

Table 8. Information of adjuvant antiviral therapy

Variables	Treated (n = 747)	
Interval between HCC therapy and antiviral therapy, months		
Mean(SD)	16.8	(18.0)
Median(IQR)	10.2	(3.3 to 24.6)
Duration of antiviral therapy, months		
Mean(SD)	18.0	(12.6)
Median(IQR)	16.3	(9.6 to 23.5)
Antiviral medicines, No. (%)		
Entecavir	489	(65.5)
Lamivudine	161	(21.6)
Telbivudine	67	(9.0)
Other*	30	(4.0)

*Other antiviral medication were including adefovir dipivoxil, tenofovir, lamivudine combined adefovir dipivoxil , peginterferon, interferon, entecavir combined adefovir dipivoxil or telbivudine combined adefovir dipivoxil

Baseline characteristics

Table 9 shows the baseline characteristics of patients before and after propensity score matching. Before propensity score matching, patients who received antiviral therapy were younger (79.1% of treated patients less than 65 years of age vs. 73.5% of untreated patients less than 65 years of age), had a higher percentage of clinical stage I or II HCC (88.8% in treated patients vs. 84.2% in untreated patients), had received RFA treatment(15.4% in treated patients vs. 11.2% in untreated patients), and suffered from cirrhosis(67.3% in treated patients vs. 54.4% in untreated patients), compared with the untreated patients.

To eliminate the effect of confounders, we used PS matching. The Kernel density plot of propensity score is shown in the supplementary figure 2. Propensity score matching yielded 747 matched pairs of study patients (747 treated and 2,595 untreated patients). No significant differences were observed between treated and untreated matched groups in terms of baseline characteristics. However, patients who received antiviral therapy also had a higher percentage of cirrhosis than patients who did not use anti-HBV agents (67.3 % in user vs. 61.2% in non-user).

Table 9. Baseline characteristics of curative HCC patients treated with antiviral therapy compared with untreated patients

	Before propensity score matching				After propensity score matching			
	Treated (n=747)	Untreated (n=3,831)	Standardized Difference (%)	P value	Treated (n=747)	Untreated (n=2,595)	Standardized Difference (%)	P value
Gender (%)								
Male	83.5	81.2		0.13	83.5	84.2		0.30
Female	16.5	18.8	6.2		16.5	15.8	1.9	
Age, mean (SD), y	55.3(11.1)	56.0(12.5)			55.3(11.1)	55.5(12.0)		
18-49	30.4	30.1	0.7	0.08	30.4	30.4	0.0	0.96
50-64	48.7	43.4	10.7		48.7	46.5	4.5	
65+	20.9	26.5	13.3		20.9	23.1	5.4	
Clinical stage (%)								
I	61.2	57.3	7.9	0.005	61.2	61.0	0.4	0.45
II	27.6	26.8	1.7		27.6	27.9	0.7	
III	11.2	15.8	13.5		11.2	11.1	0.5	
Curative treatment (%)								
Liver resection	81.8	84.3	6.6	0.001	81.8	83.4	4.3	0.90
PEI	2.8	4.5	9.0		2.8	3.0	1.4	
RFA	15.4	11.2	12.3		15.4	13.5	5.3	
Liver disease (%)								
Alcoholic liver disease	4.3	4.1	0.8	0.84	4.3	3.7	3.0	0.50
Cirrhosis of liver without mention of alcohol	67.3	54.4	26.7	<.001	67.3	61.2	12.8	0.34
Complications of liver disease (%)								
Ascites	3.9	4.0	0.6	0.89	3.9	3.7	1.2	0.80
Hepatic encephalopathy	2.8	3.1	1.7	0.67	2.8	2.8	0.2	0.92
Esophageal varices	4.6	4.2	2.0	0.62	4.6	4.4	1.0	0.89
Hapatorenal syndrome	<0.4*	0.4	3.0	0.49	<0.4*	0.2	0.7	0.72
Co-morbidity (%)								
Myocardial infarction	0.8	0.5	4.2	0.25	0.8	0.5	3.2	0.97
Congestive heart failure	1.5	2.1	4.7	0.27	1.5	1.2	2.8	0.37
Peripheral vascular disease	0.9	1.2	2.8	0.50	0.9	0.9	0.1	0.85
Cerebrovascular disease	4.1	4.2	0.3	0.95	4.1	3.6	2.9	0.52
Dementia	0.7	0.5	1.9	0.62	0.7	0.5	1.7	0.78
Chronic pulmonary disease	7.0	8.0	3.8	0.35	7.0	6.9	0.1	0.74
Rheumatic disease	1.3	1.0	3.0	0.44	1.3	1.1	2.0	0.78
Peptic ulcer disease	23.3	22.7	1.4	0.72	23.3	22.4	2.2	0.56
Diabetes mellitus	21.3	21.4	0.3	0.94	21.3	20.8	1.1	0.79
Hemiplegia or paraplegia	<0.4*	0.4	4.6	0.31	<0.4*	0.3	3.7	0.48
Renal disease	3.1	3.7	3.3	0.42	3.1	2.9	1.1	0.67
Calendar year								
2004	6.7	9.3	9.6	<.001	6.7	7.4	2.9	0.99
2005	6.4	11.7	18.5		6.4	7.7	5.0	
2006	10.6	13.2	8.1		10.6	12.1	4.7	
2007	12.2	14.8	7.7		12.2	13.1	2.8	
2008	18.3	16.7	4.2		18.3	18.4	0.2	
2009	22.9	17.7	12.8		22.9	21.2	4.2	
2010	22.9	16.5	16.2		22.9	20.1	6.8	

*The exact number of patients below 3 are not specified, in accordance with Taiwan privacy regulations

HCC progression and all cause mortality

All patients were followed up for a median of 33.0 months (IQR: 18.7 to 53.3 months), with the exception of the 1,018 (22.2%) patients who died and 2,445 (53.4%) patients who progressed. Table 10 presents the results of treatment effect for HCC progression and all cause mortality. Before adjusted confounding factors and immortal time bias, the treated patients had a lower risk of HCC progression (hazard ratio [HR], 0.45; 95%CI, 0.39-0.51) and all-cause mortality (HR, 0.53; 95%CI, 0.43-0.65) than the untreated group. After using time-dependent exposure to eliminate immortal time bias, the treated patients had a higher risk of HCC progression (HR, 1.15; 95%CI, 1.01-1.32) as well as a similar risk of all-cause mortality (HR, 1.09; 95%CI, 0.88-1.35) than the untreated group.

When Cox proportional hazard models were used a robust variance estimator and incorporated time-dependent exposure, the adjusted hazard ratio of treated patients compared to untreated patients were 1.19 (95%CI, 1.03-1.37) for HCC progression and 1.22 (95%CI, 0.98-1.51) for all cause mortality. When Cox proportional hazard models were stratified on the matched pairs and incorporated time-dependent exposure, the adjusted hazard ratio of treated patients compared to untreated patients were 1.01 (95%CI, 0.85-1.20) for HCC progression and 1.07 (95%CI, 0.83-1.38) for all cause mortality. After adjusting for all covariates and incorporated time-dependent exposure, the reduction in HCC progression (treated patients compared with untreated patients, HR, 1.00; 95%CI, 0.87 -1.15) and all cause mortality (treated patients compared with untreated patients, HR, 0.98; 95%CI, 0.79 -1.22) were comparable between the two groups (Table 10).

Sensitive analyses yielded similar results, the sub-cohort of patients who were alive

with cancer-free status at least one year after receiving curative treatment (HCC progression: hazard ratio [HR], 1.49; 95%CI, 1.23 - 1.82; all cause mortality: HR, 1.29; 95%CI, 0.90 - 1.86), the sub-cohort of patients with liver resection (HCC progression: HR, 1.60; 95%CI, 1.33 - 1.93; all cause mortality: HR, 1.62; 95%CI, 1.20 - 2.20) and the sub-cohort of patients who were both with liver resection and alive with cancer-free status at least one year (HCC progression: HR, 1.55; 95%CI, 1.23 - 1.97; all cause mortality: hazard ratio, 1.07; 95%CI, 0.68 - 1.67) (Table 11).

In the stratified analyses, we did not find that adjuvant antiviral therapy was effective at decreasing the risks of cancer progression and all cause mortality among patients who differed in terms of age, tumor status, liver disease and DM, except female patients for all cause mortality (treated patients compared with untreated patients, HR, 0.43; 95%CI, 0.22 -0.85) (Figure 16).

Figure 17 shows the influence of unmeasured HBV DNA level on HCC progression. We assumed that the prevalence of high HBV DNA level in untreated patients was 30% and the risk ratio of high HBV DNA level and HCC progression was 2.55. When prevalence of high HBV DNA level in treated patients is higher than 65%, the true effect would be toward the protective.

Table 10. Hazard ratio for HCC progression and all cause mortality, comparing untreated and treated patients

Outcome	Untreated(n=3,831)	Treated(n=747)
HCC progression		
No. of event	2,203	242
At risk person-years	8439.8	1093.6
Immortal person-years	0	1045.5
Time-fixed analysis		
Total person-years	8439.8	2139.1
Incidence rate [a]	261.0	113.1
Hazard ratio(95%CI)		
Crude	1.00	0.45 (0.39 to 0.51)
Time-dependent analysis		
Total person-years	9485.3	1093.6
Incidence rate [a]	232.3	221.3
Hazard ratio(95%CI)		
Crude [b]	1.00	1.15 (1.01 to 1.32)
Adjusted [c]	1.00	1.19 (1.03 to 1.37)
Adjusted [d]	1.00	1.01 (0.85 to 1.20)
Adjusted [e]	1.00	1.00 (0.87 to 1.15)
All cause mortality		
No. of event	921	97
At risk person-years	12018.7	1339.7
Immortal person-years	0	1045.5
Time-fixed analysis		
Total person-years	12018.7	2385.2
Incidence rate [a]	76.6	40.7
Hazard ratio(95%CI)		
Crude	1.00	0.53 (0.43 to 0.65)
Time-dependent analysis		
Total person-years	13064.2	1339.7
Incidence rate [a]	70.5	72.4
Hazard ratio(95%CI)		
Crude [b]	1.00	1.09 (0.88 to 1.35)
Adjusted [c]	1.00	1.22 (0.98 to 1.51)
Adjusted [d]	1.00	1.07 (0.83 to 1.38)
Adjusted [e]	1.00	0.98 (0.79 to 1.22)

[a] Cumulative incidence rate per 1,000 person years

[b] Crude Hazard Ratio was used time-dependent exposure.

[c] Adjusted Hazard Ratio was based on propensity score matching, incorporated time-dependent exposure and adjusted for cirrhosis. Cox proportional hazards model were used a robust variance estimator accounting for the clustering within matched sets.

[d] Adjusted Hazard Ratio was based on propensity score matching, incorporated time-dependent exposure and adjusted for cirrhosis. Cox proportional hazards model stratified on the matched sets.

[e] Adjusted Hazard Ratio was based on multivariable adjustment for all covariates and incorporated time-dependent exposure.

Table 11. Sensitivity analyses of HCC progression and all cause mortality, comparing untreated and treated patients

Study group/Outcome	N	Event	Person-Years	Incidence rate [a]	Adjusted Hazard Ratio(95%CI)[b]	Adjusted Hazard Ratio(95%CI)[C]	Adjusted Hazard Ratio(95%CI)[d]
Patients with cancer-free status at least one year							
HCC progression							
Untreated patients	2,528	952	5277.4	180.4	1.00	1.00	1.00
Treated patients	644	161	1430.6	112.5	1.49 (1.23 to 1.82)	0.83 (0.63 to 1.08)	1.09 (0.91 to 1.29)
All cause mortality							
Untreated patients	2,528	316	6880.5	45.9	1.00	1.00	1.00
Treated patients	644	47	1604.8	29.3	1.29 (0.90 to 1.86)	0.86 (0.53 to 1.40)	0.78 (0.57 to 1.08)
Patients receiving liver resection							
HCC progression							
Untreated patients	3,229	1,773	7527.5	235.5	1.00	1.00	1.00
Treated patients	611	186	1805.2	103.0	1.60 (1.33 to 1.93)	0.85 (0.65 to 1.11)	1.04 (0.89 to 1.21)
All cause mortality							
Untreated patients	3,229	758	10326.9	73.4	1.00	1.00	1.00
Treated patients	611	71	2000.7	35.5	1.62 (1.20 to 2.20)	1.14 (0.78 to 1.67)	1.04 (0.81 to 1.34)
Patients receiving liver resection and with cancer-free status at least one year							
HCC progression							
Untreated patients	2,217	802	4795.9	167.2	1.00	1.00	1.00
Treated patients	533	125	1222.3	102.3	1.55 (1.23 to 1.97)	0.93 (0.68 to 1.26)	1.14 (0.94 to 1.38)
All cause mortality							
Untreated patients	2,217	254	6197.3	41.0	1.00	1.00	1.00
Treated patients	533	32	1362.1	23.5	1.07 (0.68 to 1.67)	0.67 (0.39 to 1.16)	0.85 (0.58 to 1.24)

[a] Cumulative incidence rate per 1,000 person years

[b] Adjusted Hazard Ratio was based on propensity score matching, incorporated time-dependent exposure and adjusted for cirrhosis. Cox proportional hazards model were used a robust variance estimator accounting for the clustering within matched sets.

[c] Adjusted Hazard Ratio was based on propensity score matching, incorporated time-dependent exposure and adjusted for cirrhosis. Cox proportional hazards model stratified on the matched sets.

[d] Adjusted Hazard Ratio was based on multivariable adjustment for all covariates.

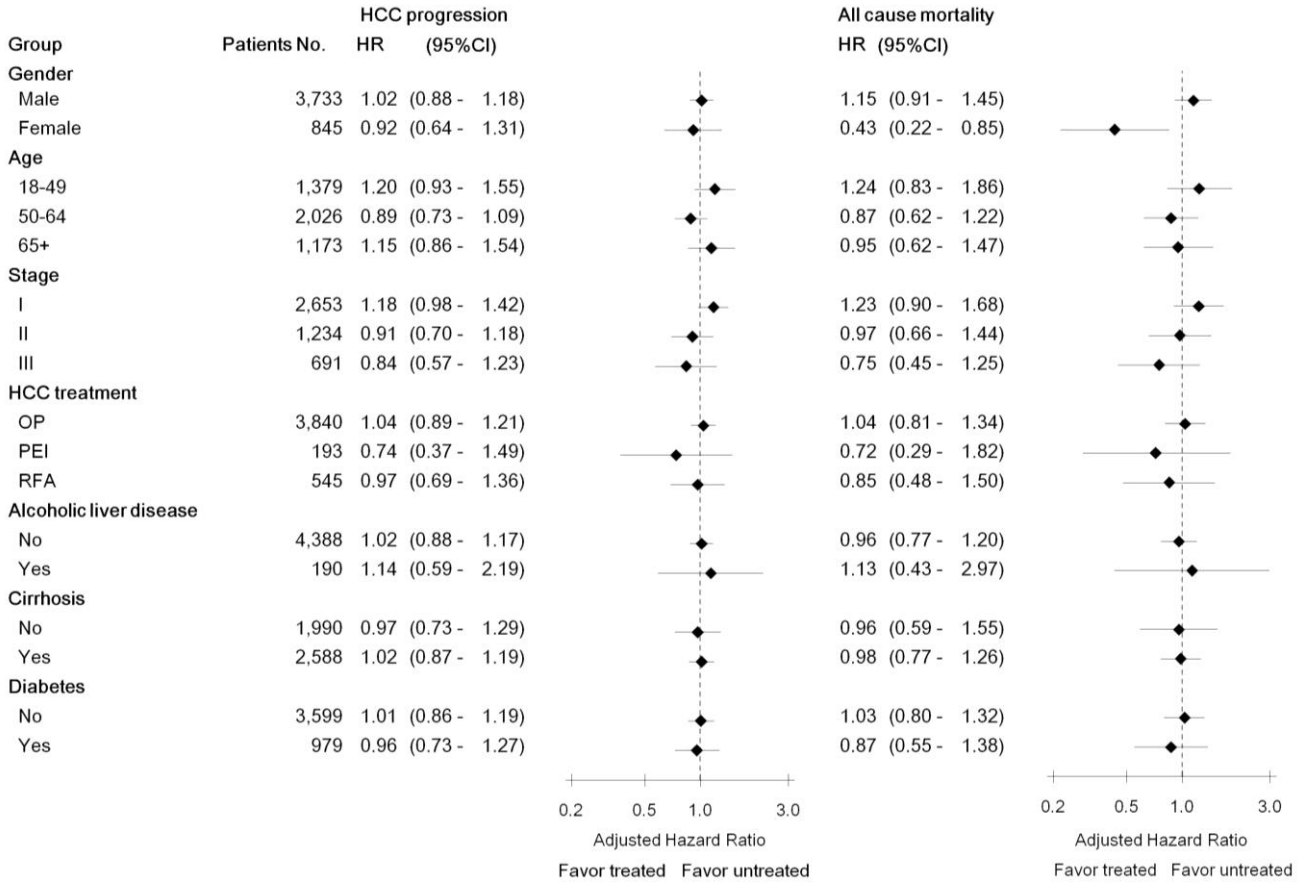


Figure 16. Subgroup analyses comparing treated and untreated on HCC progression and all cause mortality of HBV-related HCC patients by adjusted hazard ratio.

Multivariable Cox proportional hazards analyses was adjusted for sex, age, stage, calendar year, curative therapy, alcoholic liver disease, cirrhosis of liver without mention of alcohol, ascites, hepatic encephalopathy, esophageal varices, hapatorenal syndrome, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, diabetes mellitus, hemiplegia or paraplegia and renal disease.

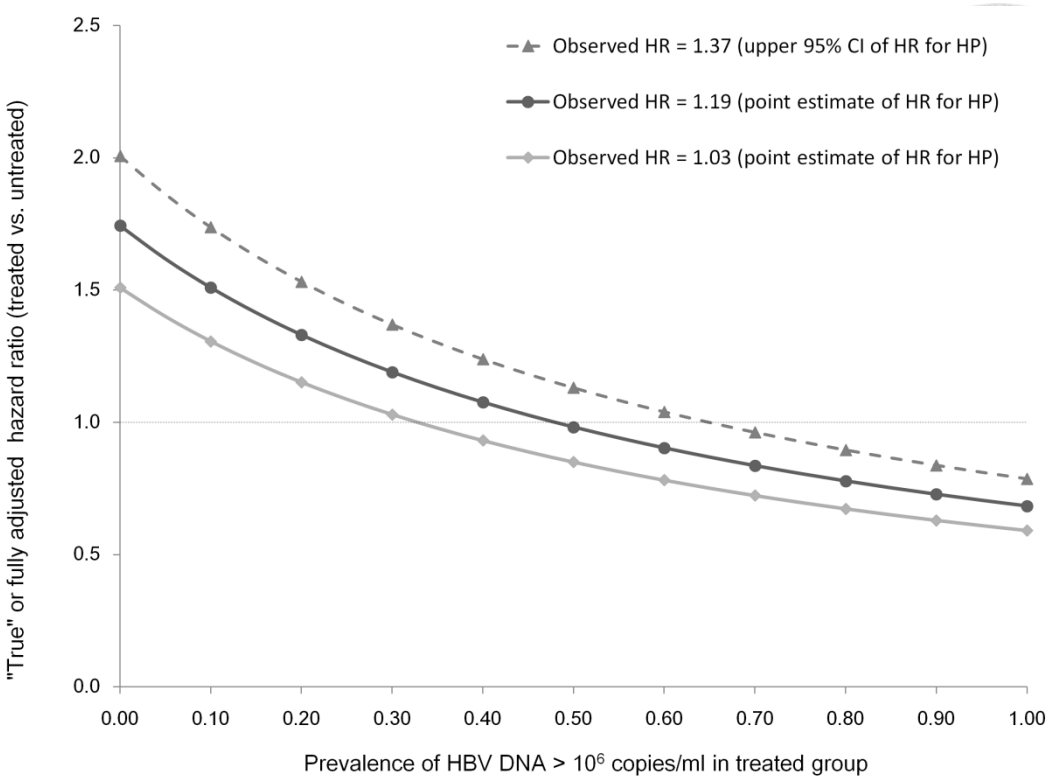


Figure 17. Sensitivity analysis to clarify the influence of unmeasured HBV DNA level on HCC progression.

The observed HRs were based on the main analysis of HCC progression estimation.

Relationship between start time of antiviral therapy and HCC progression and all cause mortality

Table 12 shows associations between the start time of antiviral therapy and HCC progression and all cause mortality. We found no association between these. However, for HCC progression, the adjusted HRs was slightly lower among patients who received the first prescription of antiviral therapy within the first six months following HCC treatment (hazard ratio, 0.82, 95%CI: 0.69-1.00).

Table 12**.** Hazard ratio for HCC progression and all cause mortality, comparing untreated patients and patients who received adjuvant antiviral therapy at different time points

Start time of antiviral therapy from HCC treatment	No of patients	HCC progression		All cause mortality	
		No of event	HR(95%CI)*	No of event	HR(95%CI)*
Untreated	3,831		Reference		Reference
0 to 6 months	274	108	0.82 (0.68 to 1.00)	51	1.01 (0.76 to 1.35)
6 to 12 months	144	55	1.08 (0.83 to 1.43)	22	0.98 (0.64 to 1.51)
12 to 24 months	136	37	1.17 (0.84 to 1.63)	8	0.61 (0.30 to 1.23)
24+ months	193	42	1.88 (1.36 to 2.60)	16	1.28 (0.77 to 2.13)

*Multivariable Cox proportional hazards analyses was adjusted for sex, age, stage, calendar year, curative therapy, alcoholic liver disease, cirrhosis of liver without mention of alcohol, ascites, hepatic encephalopathy, esophageal varices, hapatorenal syndrome, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, diabetes mellitus, hemiplegia or paraplegia and renal disease.

CHAPTER 6 DISCUSSIONS

6.1 Effectiveness research of lamivudine or interferon/peginterferon in Chronic Hepatitis B patients

This study confirmed the effectiveness of finite-period lamivudine and interferon or peg-interferon therapies in reducing the incidence of HCC and mortality among Taiwanese Chronic hepatitis B patients. Lamivudine (LAM) and interferon (IFN) are first-generation antiviral agents used in the treatment of CHB.[6] Previous studies have clearly demonstrated the efficacy of these regimens in suppressing HBV replication and in improving hepatitis activity index during or immediately after the therapy periods among chronic B patients with hepatitis B viral replication and active liver inflammation.[1, 72] However, their long-term effectiveness in reducing cirrhosis, HCC, and liver decompensation, as well as their ability to prolong survival has only been examined in clinical studies with small sample sizes. One previous meta-analysis study revealed that both forms of therapy provide benefits in reducing the incidence of HCC over the short term (relative risk: interferon, approximately 0.6; lamivudine, approximately 0.6;),[73] and recent clinical observations have provided evidence to support the efficacy of long-term maintenance antiviral (entecavir or tenofovir) therapy in reducing HCC development among patients with advanced liver disease, particularly liver cirrhosis (hazard ratios: 0.5-0.7).[35, 36] As a result, many developed countries now advocate maintenance antiviral therapy over an indefinite period, until HBsAg clearance. Such policies are reasonable and affordable in areas with low endemic HBV rates. However, in many Asia Pacific countries, where HBV infection is rampant, anti-HBV expenses can be astonishingly high. Thus, it is crucial to determine the efficacy of finite-period anti-HBV regimens in reducing end-stage

liver disease and mortality. The ultimate goal of this research was to identify the most cost-effective finite-period anti-HBV therapies for HBV endemic areas with health care funding constraints.

Several recent studies investigating the effectiveness of finite-period interferon in mitigating the incidence of end-stage liver disease and mortality produced inconsistent conclusions.[10-12, 22, 28] Two observational studies supported a decrease in HCC incidence or mortality (risk ratios or rate ratio: 0.15-0.30); however, other studies did not. The inconsistent conclusions may be due to a small number of cases. Moreover, the long-term effects of finite-period lamivudine have yet to be investigated. Thus, a large-scale study with sufficient follow-up is required to determine the relative efficacy of these two finite-period anti-HBV regimens. From this perspective, this present study is unique in that it demonstrates that the beneficial effects of finite-period not only interferon therapy but also lamivudine treatment were maintained even after five years, despite the discontinuation of therapy. The degree to which HCC or mortality was reduced by LAM or IFN reached or exceeded 30 to 75% that of the untreated controls.

Both oral NUCs and IFN have been approved and recommended as first-line therapies for CHB; however, they each have their own advantages and disadvantages with regard to treatment strategies and costs. For example, IFN-based therapy requires subcutaneous injection and has been associated with various adverse effects. Therefore, this type of therapy is adopted in fewer than 5% of treatment cases worldwide. Nonetheless, this strategy modulates the host immune response to HBV infection, such that the treatment period is finite and post-treatment response can be maintained in more than 80% of subjects achieving serologic responses.

EASL guidelines advocate finite interferon therapy for CHB patients.[74] Our data provides evidence to support the recommendation of IFN-based treatment for general CHB patients, as results showed IFN-based therapies to be effective in reducing HCC incidence and mortality. Moreover, our data also reveals additional evidence of effectiveness of finite period LAM therapy in reducing HCC and mortality among CHB patients. Specifically, the reduction afforded by LAM reached 25% to 50% and that of IFN reached 75 to 90%.

Both IFN and oral NUCs have both been approved and recommended as first-line therapies for CHB; however, information related to comparative effectiveness remains limited, and existing results are inconsistent. Thus, exploring the comparative benefits of IFN and oral NUCs therapy may be a worthwhile topic for future research. In August 2008, authorities in Taiwan updated NUC therapy to include entecavir for HBV patients. The efficacy of this new treatment regimen could also be investigated in future studies and compared with other anti-HBV regimens.

We adopted a non-user comparator to investigate the long-term effectiveness of antiviral therapies; however, this strategy is prone to selection bias and/or indication bias. To limit or decrease the effects of potential biases, we identified participants who were diagnosed with CHB and also received an ALT test at least twice during a single year. We compared the long-term outcomes of our study groups with outcomes from a community cohort of HBsAg carriers (REVEAL study), who were expected to present a lower percentage of chronic active hepatitis B than those recruited from hospitals. In the community-based REVEAL-HBV study, the cumulative incidence rates of HCC and mortality were 3.9 and 8.3 (per 1000 person-years), respectively [75]. In contrast, the subjects in our study were found to have a higher cumulative incidence rate of

HCC and mortality (approximately: 15-21 per 1000 person-years). Thus, the patients we identified were more likely to be active hepatitis B patients and thus better suited for a comparison with treatment groups.

Our study showed that lamivudine treated patients presented a high percentage of liver disease and liver disease complication, compared with untreated patients among our participants. Hence, either Cumulative mortality rate or incidence rate of HCC among treated patients should be higher than untreated patients. However, when we compared the cumulative incidence rates of HCC and mortality between patients treated with lamivudine and untreated patients, there are different amount of risk for different outcome. We assumed that this phenomenon of cumulative incidence rate of HCC may be induced by competing death. To approve this assumption, all patients were followed until the date of any events or study end date. During 7 years of follow-up period, we found that 650 patients (5.8%) with lamivudine and 4,818 untreated patients (5.2%) may be unobserved HCC incidence because these patients died before the diagnosis of HCC. A lower percentage of HCC incidences among lamivudine treated patients could probability not be explained by competing death.

6.2 Effectiveness research of adjuvant antiviral therapy in hepatitis B virus-related hepatocellular carcinoma patients following curative treatment

This cohort study evaluated the association between adjuvant antiviral therapy and the rates of HCC progression or all cause mortality of HBV-related HCC patients. Outcomes were determined based on clear surgical margins and clinico-pathological features. This study found that adjuvant antiviral therapy was not effective at decreasing HCC progression and all cause mortality. Furthermore, this study is to our knowledge the first to consider whether the start time of antiviral therapy influences the risk of HCC progression and all cause mortality. The interval length between initiation of antiviral therapy and first-line curative treatment did not show a significant association with all cause survival; however, when antiviral therapy was initiated earlier, adjusted HRs of HCC progression were lower for each treatment group.

The effects of adjuvant antiviral therapies for HBV-related HCC patients have been studied only on a limited basis. The most commonly reported approach has been interferon-based treatment. [43-45] With regard to current standardized anti-HBV agents, research investigating nucleoside analogue therapy, including lamivudine or entecavir, has yielded inconclusive results. [13, 14, 17, 47, 48] A recent nationwide study in Taiwan found that nucleoside analogues treatments were significantly associated with HCC recurrence for patients receiving liver resection. [49] However, the effects were not found in our study. Previous studies have indicated the results of this recent nationwide study may exaggerate the apparent survival advantage of this treatment due to biases. [50, 51] We will try to identify bias in this study as well as verify and quantify how the biases influence the treatment effect by replicating Dr.

Wu and colleagues' study using the Long-Form database of the Taiwan Cancer Registry (LF-TCR).

In this recent nationwide study, the first question to be addressed is selection bias. The authors stated that to ensure a homogeneous sample of patients by selecting only those who had received liver resection. Even if patients received the same pattern of treatment, their disease severity and treatment effect (whether all of the patients were cured after receiving resection) still would be very different. For example, previous studies have reported that 74 % of patients who receive liver resection are in the early stage of the disease, while 22% to 25% are in advanced stages.[76] In addition, the authors considered the drug effect period by excluding patients who received antiviral therapy for fewer than 90 days; however, this approach might introduce selection bias (i.e. selection of cases that responded well to antiviral therapy as well as survived the first 90 days after the date of the first prescription). We believe that this study may have a potential risk of selection bias following above inclusion and exclusion criteria.

In contrast with the previously mentioned study, we certified that HCC patients had been therapeutically cured after undergoing the first-course of HCC treatment by only considering patients who had received curative HCC resection and adopting additional strict inclusion criteria. Specifically, this study only included patients if they had clear surgical margins and early-stage cancer. In addition, we did not exclude patients who received antiviral therapy for fewer than 90 days and who were with follow-up for less than 3 months (Figure 18). Table 13 shows that 44% risk reduction for HCC progression to antiviral therapy replicating the previous nationwide study (HR: 0.56, 95%CI, 0.47-0.65) following old inclusion and exclusion criteria. After we re-identified inclusion and exclusion criteria, the hazard ratio was slightly increased

(HR: 0.76, 95%CI, 0.67-0.88).

After identifying the inclusion and exclusion criteria, the next questions would be confounding. Even thought we tried to restrict criteria and lead to similar participants, clinico-pathological HCC status (tumor size and clinical stage) may influence the decision to administer antiviral therapy and also influences the risk of subsequent recurrence of liver cancer. For example, our study showed that antiviral-treated patients were with an early stage of HCC, compared with untreated patients among our participants. Certain baseline characteristics are inherently associated with a lower risk of HCC recurrence and mortality. Therefore, certain clinico-pathological factors of HCC would be probably to confound results by biasing the effect estimate towards a protective effect. However, we observed that the hazard ratio was slightly decreased after adjusting all baseline characteristics (HR: 0.56, 95%CI, 0.47-0.65). To verify the influence of each covariate on treatment effect, we began by entering each covariate individually into a Cox proportional hazard model which had adjusted treatment. Table 14 shows the hazard ratios for HCC progression after adjusting each covariate. As previously noted, the increased hazard ratio was observed after further adjustment for clinical stage. Nevertheless, the increased hazard ratios were not persisted after adjusting liver disease or complications of liver disease. Hence, in addition to clinico-pathological HCC status, liver disease may be another potential confounding to be adjusted.

The final bias in this recent nationwide study is immortal time bias. The authors stated that to minimize immortal time bias, they arbitrarily defined the start date of antiviral therapy as the index date for the exposed group. Although this approach can avoid misclassified immortal time, it may introduce excluded immortal time (i.e.

selection bias).[56] Previous studies have shown that results can be biased by either misclassified immortal time or excluded immortal time in favor of treatment, with a shift in the estimation toward a protective effect.[57] We used time-dependent analysis to eliminate immortal time bias and observed that corrected hazard ratio was 1.13 (95%CI, 0.98 to 1.30).

The different inclusion criteria, additional information used to adjust for clinico-pathological status and immortal time bias might explain the inconsistent results between the previously mentioned study and our study. The effect of adjuvant antiviral therapy still needs further evaluation and validation.

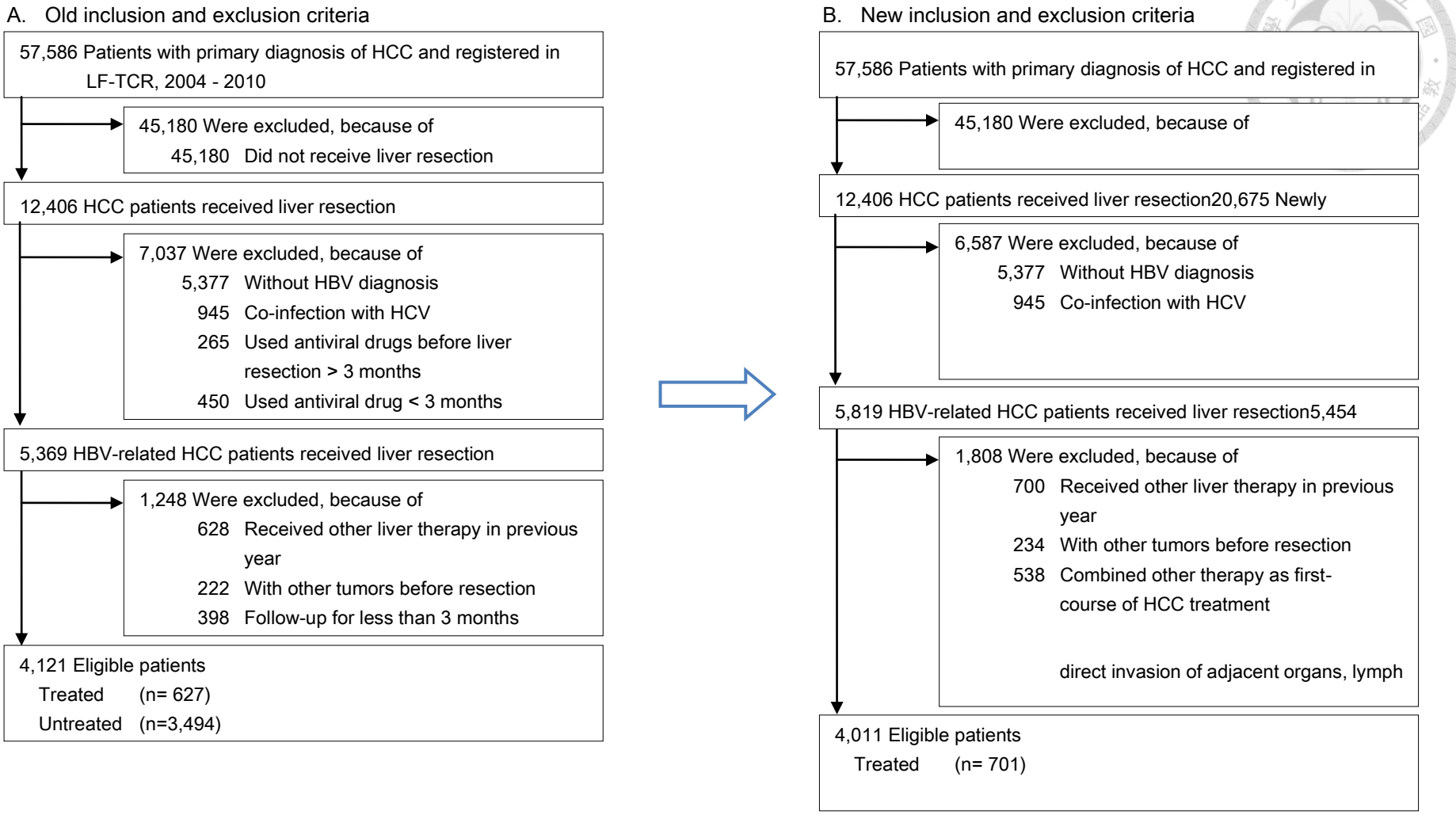


Figure 18. Flow diagram of replicating study

Table 13. Hazard ratio for HCC progression, comparing untreated patients and patients who received adjuvant antiviral therapy

		Hazard Ratio(95%CI)[b]
	Old inclusion and exclusion criteria	0.56 (0.47 to 0.65)
Step 1.	New inclusion and exclusion criteria	0.76 (0.67 to 0.88)
Step 2.	Adjusted all covariates	0.72 (0.63 to 0.83)
Step 3.	Adjusted all covariates and Time varying exposure	1.13 (0.98 to 1.30)

Table 14. Hazard ratio for HCC progression, comparing untreated patients and patients who received adjuvant antiviral therapy

	Treatment effect
	Hazard Ratio(95%CI)
Crude	0.76 (0.67 to 0.88)
Gender	0.76 (0.66 to 0.88)
Age	0.77 (0.67 to 0.88)
Clinical stage	0.78 (0.68 to 0.90)
Liver disease	
Alcoholic liver disease	0.76 (0.66 to 0.88)
Cirrhosis of liver without mention of alcohol	0.71 (0.62 to 0.82)
Complications of liver disease	
Ascites	0.74 (0.64 to 0.85)
Hepatic encephalopathy	0.74 (0.64 to 0.85)
Esophageal varices	0.74 (0.65 to 0.86)
Hapatorenal syndrome	0.77 (0.67 to 0.89)
Co-morbidity	
Myocardial infarction	0.76 (0.66 to 0.88)
Congestive heart failure	0.77 (0.67 to 0.88)
Peripheral vascular disease	0.77 (0.67 to 0.88)
Cerebrovascular disease	0.77 (0.67 to 0.88)
Dementia	0.76 (0.67 to 0.88)
Chronic pulmonary disease	0.77 (0.67 to 0.88)
Rheumatic disease	0.77 (0.67 to 0.88)
Peptic ulcer disease	0.76 (0.66 to 0.88)
Diabetes mellitus	0.77 (0.67 to 0.88)
Hemiplegia or paraplegia	0.76 (0.67 to 0.88)
Renal disease	0.76 (0.67 to 0.88)

*Untreated patients were a reference group.

This is the first study to examine the association of the time interval between initiation of antiviral therapy and first-line curative treatment and HCC progression and all-cause mortality. Our finding was that when antiviral therapy was initiated earlier, adjusted HRs of HCC progression was lower for each treatment group. The lower risk associated with early use of antiviral therapy might indicate that when these therapies are prescribed within 6 months of first-line HCC treatment, they may be able to prevent the viral and inflammatory effects of viral hepatitis B and in turn prevent HCC recurrence after curative treatment. One possible explanation is that to control the activation of viral hepatitis B and achieve hepatitis B e antigen (HBeAg) seroconversion, some patients required treatment with antiviral therapy for more than 1 year [1]. The incidence of late recurrence increases at 3 years after curative treatment [77]. Thus, for patients receiving early adjuvant antiviral therapy, specifically within 6 months of first-line HCC treatment, the duration of antiviral treatment may be sufficient to achieve antiviral response. As a result, we observed a reduction in the risk of HCC progression. Patients receiving late antiviral therapy may have already been suffering from active viral hepatitis for a long period of time prior to the initiation of anti-HBV therapy. Long-term viral hepatitis activity would probably facilitate HCC recurrence. Furthermore, late antiviral therapy was not in time and had inadequate duration to control the activation of viral hepatitis B. Finally, the negative impact was observed in late antiviral therapy. However, these results were not statistically significant. The association of start time of adjuvant antiviral therapy and HCC progression needs further evaluation and validation.

6.3 Strengths and limitations

These are the population-based, nationwide study to examine and compare the effectiveness of lamivudine and interferon or peg-interferon in the treatment of CHB as well as the effectiveness of adjuvant antiviral therapy in the treatment of HBV-related HCC. Participants were recruited from the national health insurance database and national cancer registry. Thus, the study population represents the entire earlier stages of chronic hepatitis B or HCC population and real-world clinical practice in Taiwan. Second, long-term patient outcomes were verified via linkages to the Taiwan Cancer Registry, National Health Insurance and the National Death Registry. Third, these studies employed a new user design to reduce potential selection bias, time matching and time-varying exposure to eliminate the risk of immortal time bias, and multiple strategies to assemble comparable groups of patients.

Otherwise, in the second study (HBV-related HCC patients), to investigate the effectiveness of antiviral therapy in conjunction with different forms of curative HCC treatment, we considered two major curative treatments for HCC, RFA and PEI, in addition to liver resection. In addition, to minimize the influence of confounding factors on cancer status and obtain a more accurate definition of second-line HCC treatment for HCC, we used the LF-TCR database and provided detail information on clinico-pathological HCC status and complete records of first course cancer treatment.

Nonetheless, several major limitations must be noted. First, critical clinical parameters related to the adoption of anti-HBV treatments, such as virological data (HBeAg, HBsAg, HBV DNA level, and genotype) and data related to liver function (ALT), could not be obtained from the LF-TCR and NHI databases. These criteria indicate whether treated patients suffer from more active liver disease and severe

biochemical derangement than untreated patients, potentially confounding the benefits of antiviral therapy. For instance, one unmeasured confounding factor could be HBV DNA level. Treated patients may have higher HBV DNA levels, which are expected to be associated with an increase in the risk of HCC incidence or recurrence. [71] Thus, we observed the negative impact of adjuvant antiviral therapy in the second study (HBV-related HCC patients). However, most critical clinical parameters could be obtained from hospital database or multicenter clinical registries. Future studies need accessing and linking multiple databases (such as claims database, hospital database and multicenter clinical registries) to expand the pool of available data for analysis and help to investigate clinical questions.

Second, this study used untreated patients as one of control groups, which may have confounded results through indication bias. Nonetheless, efforts made to reduce this bias as described aforementioned, and the results were shown to balance the distribution of potential confounding factors. Third, the database used in this study did not provide information related to the virological or serological outcomes of CHB patients undergoing treatment. These treatment responses are strongly associated with the long-term effectiveness of anti-HBV treatment. Information related to virological and serological responses would help to better define the effectiveness of long-term treatment. Nonetheless, our findings revealed long-term effectiveness in the whole treated group. In addition, a number of residual confounding issues, including lifestyle (smoking, alcohol consumption) and socioeconomic status, were not addressed. These factors may have influenced the estimation of effects and therefore need further investigation.

Finally, our study tried to use several approach to adjust potential confounding factors including PS matching, inverse probability of treatment weighting (IPTW), standardized mortality ratio (SMR) weighting and multivariable adjustment. Even though we reported the similarity and robustness of findings from different analyses, the best suitable analysis method in our study is still uncertain. Furthermore, different approach may have their assumptions, strengths and limitations. How to select the best analysis method for different study to adjust confounding factors still require further investigation.

Otherwise, in the first study (CHB patients), the need to account for changes in drug regimens during the follow-up period necessitated the use of first-exposure-carried-forward and as-treated analyses for the presentation of outcomes. The use of as-treated analysis may have led to bias in the estimation of effectiveness due to informative censoring. The use of first-exposure-carried-forward analysis may have led to bias toward the null due to the misclassification of exposure. However, the use of multiple analytical techniques made it possible to indicate a potential range of effectiveness [54]. In addition, we also used inverse probability of censoring weighting (IPCW) to address the problem of informative censoring. Because we used a Cox proportional hazard model to estimate treatment, censoring should be calculated at each time period which are regarded as time varying covariates. However, we did not consider the time varying censoring rate and only estimated one censoring weighting by the final event status. Based on this assumption, using this inverse probability of censoring weighting (IPCW) in our study may bias the treatment effect estimate.

In the first study (CHB patients), we were interested in the comparison of multiple groups. The best approach was evaluated based on three groups together. Because we considered the time of started reimbursement and indication or contraindication are different, the analysis were used pair-wise approach to estimate effects of lamivudine and interferon, separately. In addition, we selected time matching to deal with immortal time bias. Because we did not enroll all participants in final analyses, there could probability introduce selection bias.

Otherwise, in the second study (HBV-related HCC patients), this study was the inability to directly identify HCC progression due to a lack of imaging information. To compensate, we defined HCC progression indirectly by considering the time at which the subsequent course of HCC treatment was initiated or the date of death. We certified that HCC patients had been therapeutically cured after undergoing the first-course of HCC treatment by only considering patients who had clear surgical margins. However, the information of surgical margins would have missing value in our study groups. HCC recurrence and mortality within 1 year of curative therapy were regarded as early recurrence caused by the original tumor or therapeutically uncured. Thus, any difference in survival rate detected during this period may be a result of something other than antiviral therapy. To compensate for this problem, we conducted a sensitivity analysis which considered patients who had been alive with cancer-free status at least one year after receiving curative treatment. This analysis did not however effect any change on our results. Finally, although our analyses adjusted for a number of risk factors, other residual confounding issues may have been neglected such as smoking status, drinking or healthy behaviors.

CHAPTER 7 CONCLUSION

This first population-based study provides evidence supporting the effectiveness of a finite course, first-generation, anti-HBV therapy in improving the long-term outcomes of CHB in the Asian-Pacific region. However, adjuvant antiviral therapy did not confer any benefits related to the reduction of HCC progression and all cause mortality for HBV-related HCC patients. When antiviral therapy was initiated earlier, adjusted HRs of HCC progression was lower for each treatment group. The association of antiviral therapy and HCC progression and deaths on HCC patients and the association of start time of adjuvant antiviral therapy and HCC progression still require further investigation. These findings are important for health authorities and public health workers.

REFERENCE

1. Liaw, Y.-F. and C.-M. Chu, *Hepatitis B virus infection.* The Lancet, 2009. **373**(9663): p. 582-592.
2. Lu, S.N., et al., *Secular trends and geographic variations of hepatitis B virus and hepatitis C virus-associated hepatocellular carcinoma in Taiwan.* Int J Cancer, 2006. **119**(8): p. 1946-52.
3. Chen, D.S., et al., *A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers.* Jama, 1987. **257**(19): p. 2597-603.
4. Ministry of health and welfare, *Causes of death in Taiwan, 2012*. 2012, Ministry of health and welfare: Taiwan.
5. Chang, M.-H., et al., *Universal Hepatitis B Vaccination in Taiwan and the Incidence of Hepatocellular Carcinoma in Children.* New England Journal of Medicine, 1997. **336**(26): p. 1855-1859.
6. Kao, J.H. and D.S. Chen, *Global control of hepatitis B virus infection.* Lancet Infect Dis, 2002. **2**(7): p. 395-403.
7. Mazzaferro, V., et al., *Prevention of hepatocellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis.* Hepatology, 2006. **44**(6): p. 1543-1554.
8. Poon, R., *Differentiating Early and Late Recurrences After Resection of HCC in Cirrhotic Patients: Implications on Surveillance, Prevention, and Treatment Strategies.* Annals of Surgical Oncology, 2009. **16**(4): p. 792-794.
9. Omata, M., et al., *Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma.* Hepatology International, 2010. **4**(2): p. 439-474.
10. Lin, S.-M., et al., *Interferon therapy in HBeAg positive chronic hepatitis reduces progression to cirrhosis and hepatocellular carcinoma.* Journal of Hepatology, 2007. **46**(1): p. 45-52.
11. Yuen, M.F., et al., *Long-term follow-up of interferon alfa treatment in Chinese patients with chronic hepatitis B infection: The effect on hepatitis B e antigen seroconversion and the development of cirrhosis-related complications.* Hepatology, 2001. **34**(1): p. 139-45.
12. Papatheodoridis, G.V., E. Manesis, and S.J. Hadziyannis, *The long-term outcome of interferon-α treated and untreated patients with HBeAg-negative chronic hepatitis B.* Journal of Hepatology, 2001. **34**(2): p. 306-313.
13. Yoshida, H., et al., *Safety and efficacy of lamivudine after radiofrequency ablation in patients with hepatitis B virus-related hepatocellular carcinoma.* Hepatology International, 2008. **2**(1): p. 89-94.
14. Kuzuya, T., et al., *Efficacy of antiviral therapy with lamivudine after initial treatment for hepatitis B virus-related hepatocellular carcinoma.* Journal of Gastroenterology and Hepatology, 2007. **22**(11): p. 1929-1935.
15. Piao, C.Y., et al., *Lamivudine treatment in patients with HBV-related hepatocellular carcinoma--using an untreated, matched control cohort.* Acta medica Okayama, 2005. **59**(5): p. 217-224.
16. Kubo, S., et al., *Effects of lamivudine on outcome after liver resection for hepatocellular carcinoma in patients with active replication of hepatitis B virus.* Hepatology Research, 2007. **37**(2): p. 94-100.

17. Chan, A.C.Y., et al., *Impact of Antiviral Therapy on the Survival of Patients After Major Hepatectomy for Hepatitis B Virus-Related Hepatocellular Carcinoma.* Archives of Surgery, 2011. **146**(6): p. 675-681.
18. McMahon, B.J., *The natural history of chronic hepatitis B virus infection.* Hepatology, 2009. **49**(5 Suppl): p. S45-55.
19. Merican, I., et al., *Chronic hepatitis B virus infection in Asian countries.* J Gastroenterol Hepatol, 2000. **15**(12): p. 1356-61.
20. Fattovich, G., et al., *Long-term outcome of hepatitis B e antigen-positive patients with compensated cirrhosis treated with interferon alfa. European Concerted Action on Viral Hepatitis (EUROHEP).* Hepatology, 1997. **26**(5): p. 1338-42.
21. Ikeda, K., et al., *Interferon decreases hepatocellular carcinogenesis in patients with cirrhosis caused by the hepatitis B virus: a pilot study.* Cancer, 1998. **82**(5): p. 827-35.
22. Benvegnù, L., et al., *Retrospective analysis of the effect of interferon therapy on the clinical outcome of patients with viral cirrhosis.* Cancer, 1998. **83**(5): p. 901-909.
23. Brunetto, M.R., et al., *Effect of interferon-α on progression of cirrhosis to hepatocellular carcinoma: a retrospective cohort study.* The Lancet, 1998. **351**(9115): p. 1535-1539.
24. Krogsgaard, K., G. the Long-term Follow-up Investigator, and T. Executive Team on Anti-Viral, *The long-term effect of treatment with interferon-α2a in chronic hepatitis B.* Journal of Viral Hepatitis, 1998. **5**(6): p. 389-397.
25. Di Marco, V., et al., *The long-term course of chronic hepatitis B.* Hepatology, 1999. **30**(1): p. 257-264.
26. Mazzella, G., et al., *Long-term results with interferon therapy in chronic type B hepatitis: a prospective randomized trial.* Am J Gastroenterol, 1999. **94**(8): p. 2246-2250.
27. Lin, S.M., et al., *Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection.* Hepatology, 1999. **29**(3): p. 971-5.
28. Tangkijvanich, P., et al., *Long-term effect of interferon therapy on incidence of cirrhosis and hepatocellular carcinoma in Thai patients with chronic hepatitis B.* Southeast Asian J Trop Med Public Health, 2001. **32**(3): p. 452-8.
29. Truong, B.X., et al., *Long-term follow-up of Japanese patients with chronic hepatitis B treated with interferon-alpha.* Int J Mol Med, 2005. **16**(2): p. 279-84.
30. Liaw, Y.-F., et al., *Lamivudine for Patients with Chronic Hepatitis B and Advanced Liver Disease.* New England Journal of Medicine, 2004. **351**(15): p. 1521-1531.
31. Matsumoto, A., et al., *Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2795 patients.* Hepatol Res, 2005. **32**(3): p. 173-84.
32. Papatheodoridis, G.V., et al., *Outcome of hepatitis B e antigen-negative chronic hepatitis B on long-term nucleos(t)ide analog therapy starting with lamivudine.* Hepatology, 2005. **42**(1): p. 121-9.
33. Yuen, M.F., et al., *Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without*

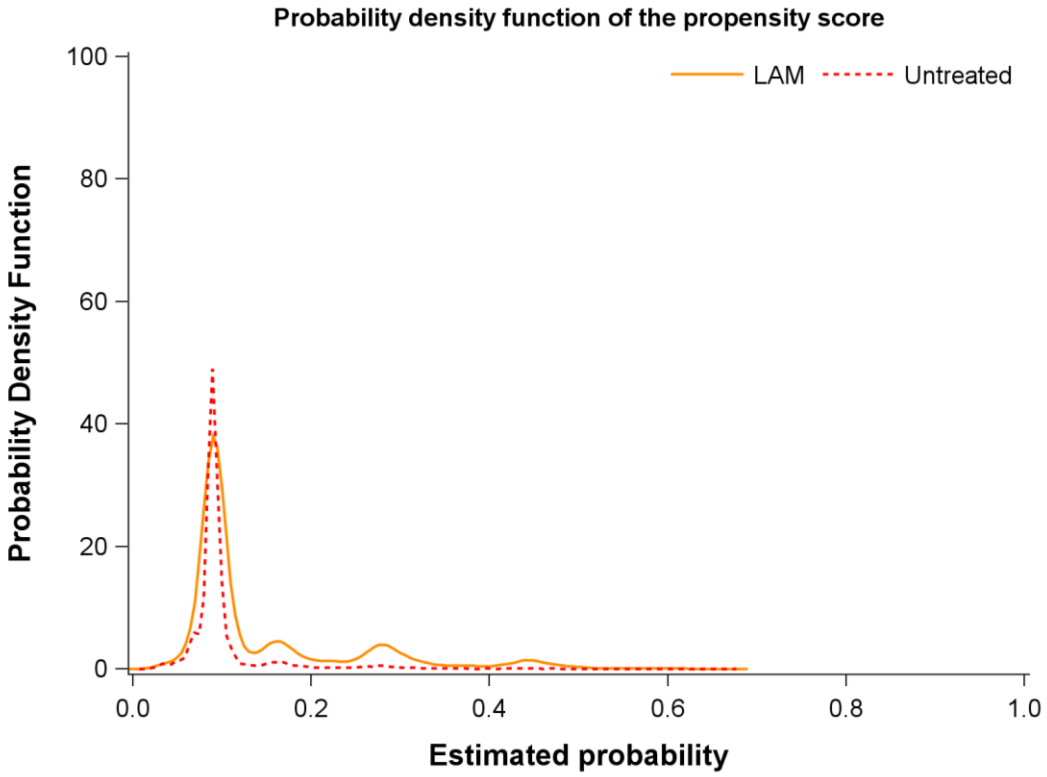
advanced disease. Antivir Ther, 2007. **12**(8): p. 1295-303.
34. Eun, J.R., et al., *Risk assessment for the development of hepatocellular carcinoma: According to on-treatment viral response during long-term lamivudine therapy in hepatitis B virus-related liver disease.* Journal of Hepatology, 2010. **53**(1): p. 118-125.
35. Hosaka, T., et al., *Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection.* Hepatology, 2013. **58**(1): p. 98-107.
36. Wong, G.L., et al., *Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis.* Hepatology, 2013. **58**(5): p. 1537-47.
37. Llovet, J.M., A. Burroughs, and J. Bruix, *Hepatocellular carcinoma.* The Lancet, 2003. **362**(9399): p. 1907-1917.
38. Llovet, J.M., *Updated treatment approach to hepatocellular carcinoma.* Journal of Gastroenterology, 2005. **40**(3): p. 225-235.
39. Germani, G., et al., *Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocelullar carcinoma: A meta-analysis.* Journal of Hepatology, 2010. **52**(3): p. 380-388.
40. Schwartz, J.D., et al., *Neoadjuvant and adjuvant therapy for resectable hepatocellular carcinoma: review of the randomised clinical trials.* The Lancet Oncology, 2002. **3**(10): p. 593-603.
41. Poon, R.T.P., *Prevention of recurrence after resection of hepatocellular carcinoma: A daunting challenge.* Hepatology, 2011. **54**(3): p. 757-759.
42. Shen, Y.-C., et al., *Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): A meta-regression approach.* Journal of Hepatology, 2010. **52**(6): p. 889-894.
43. Sun, H.-C., et al., *Postoperative interferon α treatment postponed recurrence and improved overall survival in patients after curative resection of HBV-related hepatocellular carcinoma: a randomized clinical trial.* Journal of Cancer Research and Clinical Oncology, 2006. **132**(7): p. 458-465.
44. Chen, L.T., et al., *Long-Term Results of a Randomized, Observation-Controlled, Phase III Trial of Adjuvant Interferon Alfa-2b in Hepatocellular Carcinoma After Curative Resection.* Annals of Surgery, 2011. **255**(1): p. 8-17.
45. Lo, C.M., et al., *A randomized, controlled trial of postoperative adjuvant interferon therapy after resection of hepatocellular carcinoma.* Ann Surg, 2007. **245**(6): p. 831-42.
46. Kao, J.-H. and D.-S. Chen, *Global control of hepatitis B virus infection.* The Lancet Infectious Diseases, 2002. **2**(7): p. 395-403.
47. Li, N., et al., *A Comparative Study of Antiviral Therapy After Resection of Hepatocellular Carcinoma in the Immune-Active Phase of Hepatitis B Virus Infection.* Annals of Surgical Oncology, 2010. **17**(1): p. 179-185.
48. Hung, I.F.N., et al., *Recurrence of hepatitis B-related hepatocellular carcinoma is associated with high viral load at the time of resection.* American Journal of Gastroenterology, 2008. **103**(7): p. 1663-1673.
49. Wu, C.-Y., et al., *Association between nucleoside analogues and risk of hepatitis b virus–related hepatocellular carcinoma recurrence following liver resection.* JAMA, 2012. **308**(18): p. 1906-1913.

50. Hsu, C., *Antiviral therapy and hepatitis b virus–related hepatocellular carcinoma recurrence.* JAMA, 2013. **309**(8): p. 765-765.
51. Yeh, Y.C., P.J. Chen, and M.S. Lai, *Antiviral therapy and hepatitis b virus–related hepatocellular carcinoma recurrence.* JAMA, 2013. **309**(8): p. 765-767.
52. Cox, E., et al., *Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report--Part II.* Value Health, 2009. **12**(8): p. 1053-61.
53. Berger, M.L., et al., *Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report--Part I.* Value Health, 2009. **12**(8): p. 1044-52.
54. Schneeweiss, S., *A basic study design for expedited safety signal evaluation based on electronic healthcare data.* Pharmacoepidemiol Drug Saf, 2010. **19**(8): p. 858-68.
55. Austin, P.C., *An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies.* Multivariate Behavioral Research, 2011. **46**(3): p. 399-424.
56. Lévesque, L.E., et al., *Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes.* BMJ, 2010. **340**.
57. Suissa, S., *Immortal time bias in observational studies of drug effects.* Pharmacoepidemiology and Drug Safety, 2007. **16**(3): p. 241-249.
58. Zhou, Z., et al., *Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods.* Am J Epidemiol, 2005. **162**(10): p. 1016-23.
59. Howe, C.J., et al., *Limitation of Inverse Probability-of-Censoring Weights in Estimating Survival in the Presence of Strong Selection Bias.* American Journal of Epidemiology, 2011.
60. Schneeweiss, S., *Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics.* Pharmacoepidemiol Drug Saf, 2006. **15**(5): p. 291-303.
61. *Universal Health Coverage in Taiwan*. 2011 May 2012 [cited 2012; Available from: http://www.nhi.gov.tw/Resource/webdata/21717_1_20120808UniversalHealthCoverage.pdf.
62. Taiwan Cancer Registry. *Taiwan Cancer Registry*. n.d. [cited 2012 5, April]; Bureau of Health Promotion, Department of Health, Taiwan, ROC:[Available from: http://tcr.cph.ntu.edu.tw/main.php?Page=N1.
63. Asrani, S.K., et al., *Underestimation of Liver-Related Mortality in the United States.* Gastroenterology, 2013. **145**(2): p. 375-382.e2.
64. Quan, H., et al., *Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data.* Medical care, 2005. **43**(11): p. 1130-9.
65. Cole, S.R. and M.A. Hernán, *Adjusted survival curves with inverse probability*

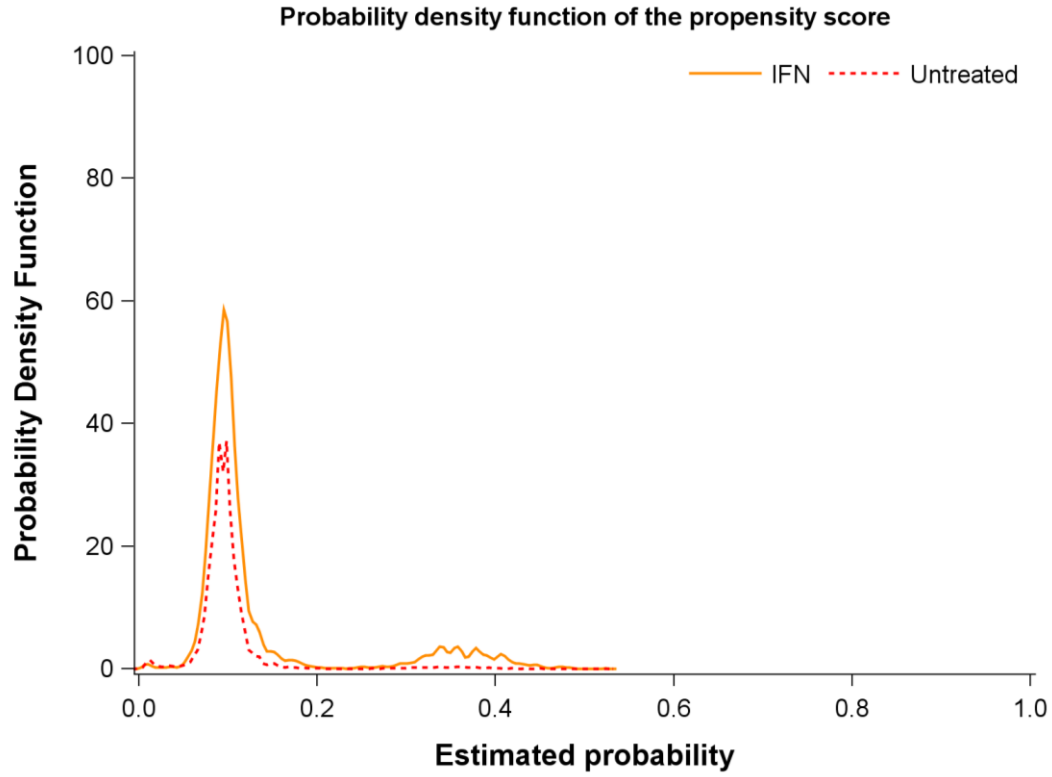
weights. Computer Methods and Programs in Biomedicine, 2004. **75**(1): p. 45-49.
66. Austin, P.C., *Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples.* Stat Med, 2009. **28**(25): p. 3083-107.
67. Williamson, E.J., A. Forbes, and I.R. White, *Variance reduction in randomised trials by inverse probability weighting using the propensity score.* Statistics in Medicine, 2014. **33**(5): p. 721-737.
68. Sato, T. and Y. Matsuyama, *Marginal structural models as a tool for standardization.* Epidemiology, 2003. **14**(6): p. 680-6.
69. Chiang, C.J., et al., *Quality assessment and improvement of nationwide cancer registration system in Taiwan: a review.* Jpn J Clin Oncol, 2015. **45**(3): p. 291-6.
70. Greene, F.L., et al., *Liver including intrahepatic bile ducts*, in *AJCC Cancer Staging Handbook*. 2002, Springer: New York. p. 131-144.
71. Wu, J.C., et al., *Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma.* J Hepatol, 2009. **51**(5): p. 890-7.
72. *Hepatitis B and C Treatments*. 2015 [cited 2015 June 10]; Available from: http://www.fda.gov/forpatients/illness/hepatitisbc/ucm408658.htm.
73. Sung, J.J., et al., *Meta-analysis: Treatment of hepatitis B infection reduces risk of hepatocellular carcinoma.* Aliment Pharmacol Ther, 2008. **28**(9): p. 1067-77.
74. *EASL clinical practice guidelines: Management of chronic hepatitis B virus infection.* J Hepatol, 2012. **57**(1): p. 167-85.
75. Chen, C.J., et al., *Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level.* Jama, 2006. **295**(1): p. 65-73.
76. *Taiwan Cancer Registry Database 2005-2007*. 2010, Taiwan Cancer Registry, Bureau of National Health Insurance, Department of Health: Taipei. p. 105.
77. Imamura, H., et al., *Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy.* J Hepatol, 2003. **38**(2): p. 200-7.

SUPPLEMENTARY

A. LAM vs. Untreated

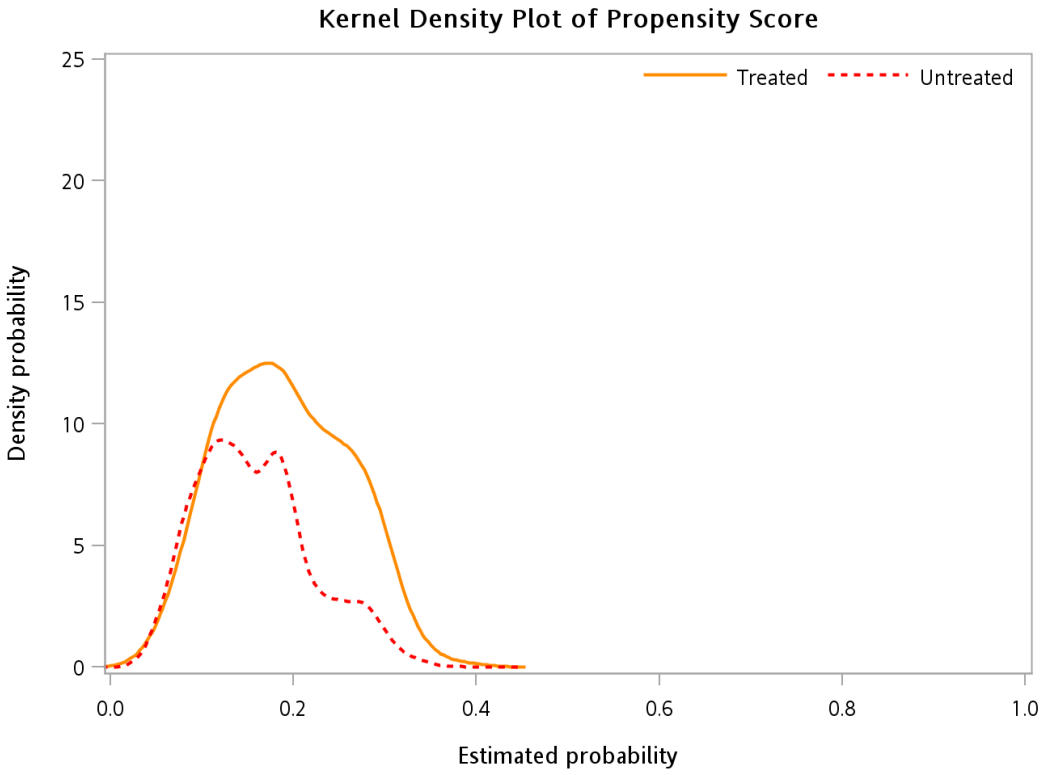


B. IFN vs. Untreated

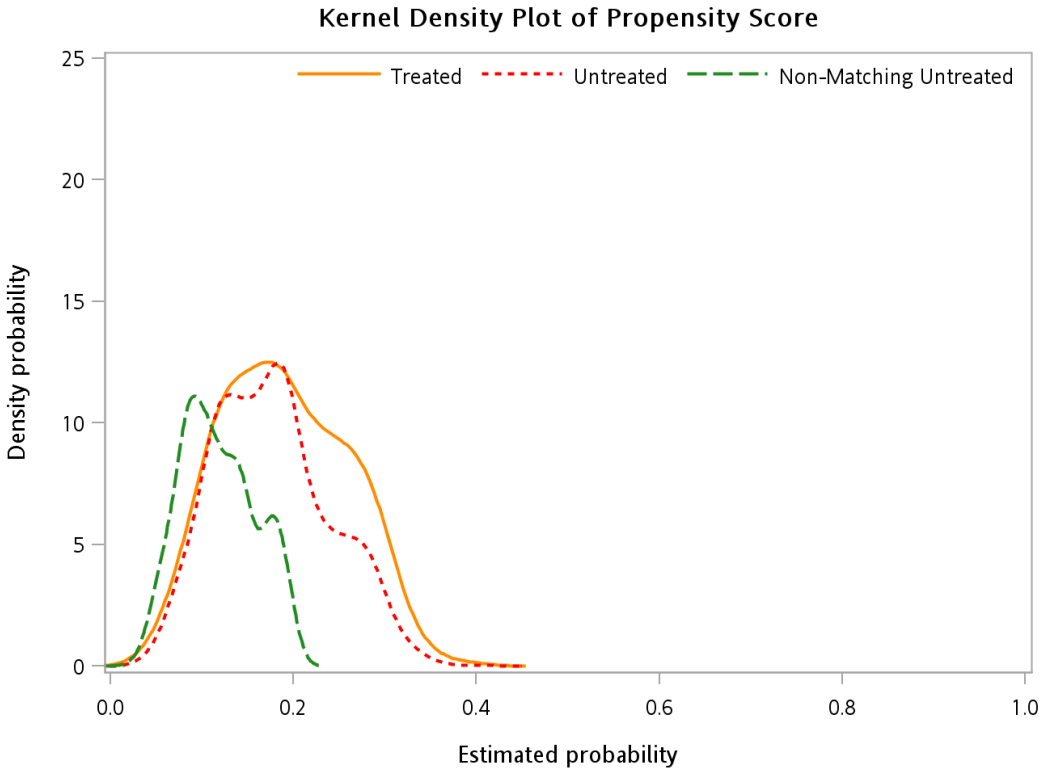


Supplementary Figure 1. Kernel density plot of the propensity score

A. Before PS matching



B. After PS matching



Supplementary Figure 2. Kernel density plot of the propensity score

Supplementary Table 1. Baseline characteristics of patients treated with lamivudine compared with untreated patients (Before covariates adjustment)

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		103160	(100.0)	91952	(100.0)	11208	(100.0)	-
FECF-Incidence(Person Years)		413289.8		365731.8		47558.1		
AT-Incidence(Person Years)		406798.3		365731.8		41066.5		
FECF-Incidence(Person Months)		4945927.6		4376790.2		569137.4		
AT-Incidence(Person Months)		4868242.3		4376790.2		491452.1		
FECF-Median follow-up time of incidence(months)	Mean(SD)	47.9(23.6)		47.6(23.7)		50.8(22.6)		<0.0001
	Median (Q1,Q3)	50.1(32.8, 67.9)		49.6(32.5, 67.5)		54.0(36.1, 69.6)		
	Median (min,max)	50.1(0.0, 83.8)		49.6(0.0, 83.8)		54.0(0.0, 83.8)		
AT-Median follow-up time of incidence(months)	Mean(SD)	47.2(23.8)		47.6(23.7)		43.8(24.0)		<0.0001
	Median (Q1,Q3)	49.0(31.7, 67.2)		49.6(32.5, 67.5)		44.3(24.1, 64.9)		
	Median (min,max)	49.0(0.0, 83.8)		49.6(0.0, 83.8)		44.3(0.0, 83.8)		
FECF-Mortality(Person Years)		426520.6		378020.1		48500.5		
AT-Mortality(Person Years)		419770.8		378020.1		41750.6		
FECF-Mortality(Person Months)		5104263.0		4523847.5		580415.5		
AT-Mortality(Person Months)		5023486.3		4523847.5		499638.8		
FECF-Median follow-up time of Mortality(months)	Mean(SD)	49.5(22.5)		49.2(22.5)		51.8(22.0)		<0.0001
	Median (Q1,Q3)	51.4(34.9, 68.4)		51.0(34.4, 68.1)		55.0(37.4, 70.1)		
	Median (min,max)	51.4(0.0, 83.8)		51.0(0.0, 83.8)		55.0(0.0, 83.8)		
AT-Median follow-up time of Mortality(months)	Mean(SD)	48.7(22.7)		49.2(22.5)		44.6(23.7)		<0.0001
	Median (Q1,Q3)	50.3(33.5, 67.9)		51.0(34.4, 68.1)		45.0(25.4, 65.4)		
	Median (min,max)	50.3(0.0, 83.8)		51.0(0.0, 83.8)		45.0(0.0, 83.8)		

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Duration of lamivudine therapy(Months)	Mean(SD)	15.1(7.9)				15.1(7.9)		
	Median (Q1,Q3)	16.6(10.8, 18.0)				16.6(10.8, 18.0)		
	Median (min,max)	16.6(0.0, 72.3)				16.6(0.0, 72.3)		
Switching	No	99615	(96.6)	91952	(100.0)	7663	(68.4)	<0.001
	Yes	3545	(3.4)			3545	(31.6)	
Calendar year	2004	22614	(21.9)	19970	(21.7)	2644	(23.6)	<0.001
	2005	21723	(21.1)	19254	(20.9)	2469	(22.0)	
	2006	18541	(18.0)	16494	(17.9)	2047	(18.3)	
	2007	19775	(19.2)	17711	(19.3)	2064	(18.4)	
	2008	11730	(11.4)	10560	(11.5)	1170	(10.4)	
	2009	3411	(3.3)	3090	(3.4)	321	(2.9)	
	2010	5366	(5.2)	4873	(5.3)	493	(4.4)	
Sex	Male	74418	(72.1)	66125	(71.9)	8293	(74.0)	<0.001
	Female	28742	(27.9)	25827	(28.1)	2915	(26.0)	
Age	Mean(SD)	39.7(13.5)		39.7(13.5)		40.2(13.2)		<0.0001
	Median (Q1,Q3)	38.0(29.0, 48.0)		38.0(29.0, 48.0)		39.0(29.0, 49.0)		
	Median (min,max)	38.0(18.0, 96.0)		38.0(18.0, 96.0)		39.0(18.0, 87.0)		
Age	18-24	12114	(11.7)	10884	(11.8)	1230	(11.0)	<0.001
	25-34	31874	(30.9)	28720	(31.2)	3154	(28.1)	
	35-44	25802	(25.0)	22947	(25.0)	2855	(25.5)	
	45-54	18095	(17.5)	15866	(17.3)	2229	(19.9)	
	55-64	9796	(9.5)	8626	(9.4)	1170	(10.4)	
	65+	5479	(5.3)	4909	(5.3)	570	(5.1)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Alcoholic liver disease	No	100020	(97.0)	89185	(97.0)	10835	(96.7)	0.0636
	Yes	3140	(3.0)	2767	(3.0)	373	(3.3)	
Cirrhosis of liver without mention of alcohol	No	94334	(91.4)	85031	(92.5)	9303	(83.0)	<0.001
	Yes	8826	(8.6)	6921	(7.5)	1905	(17.0)	
Ascites	No	101227	(98.1)	90469	(98.4)	10758	(96.0)	<0.001
	Yes	1933	(1.9)	1483	(1.6)	450	(4.0)	
Hepatic encephalopathy	No	101859	(98.7)	90898	(98.9)	10961	(97.8)	<0.001
	Yes	1301	(1.3)	1054	(1.1)	247	(2.2)	
Esophageal varices	No	101109	(98.0)	90312	(98.2)	10797	(96.3)	<0.001
	Yes	2051	(2.0)	1640	(1.8)	411	(3.7)	
Hapatorenal syndrome	No	103123	(100.0)	91919	(100.0)	11204	(100.0)	0.9916
	Yes	37	(0.0)	33	(0.0)	4	(0.0)	
Acute liver disease previous 1 year-Hospitalization	0-6	8659	(8.4)	6201	(6.7)	2458	(21.9)	<0.001
	6-12	2822	(2.7)	2390	(2.6)	432	(3.9)	
	Never	91679	(88.9)	83361	(90.7)	8318	(74.2)	
Acute liver disease previous 1 year-Emergency department visit	0-6	3716	(3.6)	2620	(2.8)	1096	(9.8)	<0.001
	6-12	1167	(1.1)	973	(1.1)	194	(1.7)	
	Never	98277	(95.3)	88359	(96.1)	9918	(88.5)	
Myocardial infarction	No	102991	(99.8)	91807	(99.8)	11184	(99.8)	0.1630
	Yes	169	(0.2)	145	(0.2)	24	(0.2)	
Congestive heart failure	No	102002	(98.9)	90920	(98.9)	11082	(98.9)	0.9858
	Yes	1158	(1.1)	1032	(1.1)	126	(1.1)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Peripheral vascular disease	No	102685	(99.5)	91522	(99.5)	11163	(99.6)	0.3289
	Yes	475	(0.5)	430	(0.5)	45	(0.4)	
Cerebrovascular disease	No	101372	(98.3)	90330	(98.2)	11042	(98.5)	0.0303
	Yes	1788	(1.7)	1622	(1.8)	166	(1.5)	
Dementia	No	102950	(99.8)	91763	(99.8)	11187	(99.8)	0.6869
	Yes	210	(0.2)	189	(0.2)	21	(0.2)	
Chronic pulmonary disease	No	98555	(95.5)	87810	(95.5)	10745	(95.9)	0.0706
	Yes	4605	(4.5)	4142	(4.5)	463	(4.1)	
Rheumatic disease	No	102236	(99.1)	91161	(99.1)	11075	(98.8)	<0.001
	Yes	924	(0.9)	791	(0.9)	133	(1.2)	
Peptic ulcer disease	No	88763	(86.0)	79700	(86.7)	9063	(80.9)	<0.001
	Yes	14397	(14.0)	12252	(13.3)	2145	(19.1)	
Diabetes	No	94020	(91.1)	83798	(91.1)	10222	(91.2)	0.8045
	Yes	9140	(8.9)	8154	(8.9)	986	(8.8)	
Hemiplegia or paraplegia	No	102927	(99.8)	91742	(99.8)	11185	(99.8)	0.6257
	Yes	233	(0.2)	210	(0.2)	23	(0.2)	
Renal disease	No	101602	(98.5)	90637	(98.6)	10965	(97.8)	<0.001
	Yes	1558	(1.5)	1315	(1.4)	243	(2.2)	
FECF - HCC incidence	No	96616	(93.7)	85935	(93.5)	10681	(95.3)	<0.001
	Yes	6544	(6.3)	6017	(6.5)	527	(4.7)	
AT - HCC incidence	No	96709	(93.7)	85935	(93.5)	10774	(96.1)	<0.001
	Yes	6451	(6.3)	6017	(6.5)	434	(3.9)	
FECF - All-cause mortality	No	94902	(92.0)	84648	(92.1)	10254	(91.5)	0.0363

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	8258	(8.0)	7304	(7.9)	954	(8.5)	
AT - All-cause mortality	No	95047	(92.1)	84648	(92.1)	10399	(92.8)	0.0071
	Yes	8113	(7.9)	7304	(7.9)	809	(7.2)	
FECF - Liver-related mortality	No	98017	(95.0)	87446	(95.1)	10571	(94.3)	<0.001
	Yes	5143	(5.0)	4506	(4.9)	637	(5.7)	
AT - Liver-related mortality	No	98128	(95.1)	87446	(95.1)	10682	(95.3)	0.3361
	Yes	5032	(4.9)	4506	(4.9)	526	(4.7)	

Supplementary Table 2. Baseline characteristics of patients treated with lamivudine compared with untreated patients (After IPTW)

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		103189.56	(100.00)	92032.14	(100.00)	11157.42	(100.00)	-
Calendar year	2004	22863.62	(22.16)	20251.52	(22.00)	2612.11	(23.41)	0.0048
	2005	21805.39	(21.13)	19398.60	(21.08)	2406.78	(21.57)	
	2006	18492.41	(17.92)	16524.47	(17.96)	1967.95	(17.64)	
	2007	19686.09	(19.08)	17614.42	(19.14)	2071.67	(18.57)	
	2008	11665.48	(11.30)	10438.01	(11.34)	1227.47	(11.00)	
	2009	3373.54	(3.27)	3034.52	(3.30)	339.03	(3.04)	
	2010	5303.02	(5.14)	4770.60	(5.18)	532.42	(4.77)	
Sex	Male	74597.38	(72.29)	66426.77	(72.18)	8170.61	(73.23)	0.0190
	Female	28592.18	(27.71)	25605.37	(27.82)	2986.80	(26.77)	
Age	Mean(SD)	39.8(13.5)		39.8(13.5)		39.6(13.4)		
	Median (min,max)	38.0(18.0, 96.0)		38.0(18.0, 96.0)		37.0(18.0, 87.0)		
Age	18-24	12109.76	(11.74)	10798.61	(11.73)	1311.15	(11.75)	0.4434
	25-34	31802.39	(30.82)	28400.86	(30.86)	3401.52	(30.49)	
	35-44	25800.77	(25.00)	23004.63	(25.00)	2796.14	(25.06)	
	45-54	18083.44	(17.52)	16156.38	(17.56)	1927.06	(17.27)	
	55-64	9839.02	(9.53)	8762.44	(9.52)	1076.59	(9.65)	
	65+	5554.19	(5.38)	4909.22	(5.33)	644.96	(5.78)	
Alcoholic liver disease	No	99877.66	(96.79)	89214.39	(96.94)	10663.27	(95.57)	<0.001
	Yes	3311.90	(3.21)	2817.75	(3.06)	494.15	(4.43)	
Cirrhosis of liver without mention of alcohol	No	93951.85	(91.05)	83980.95	(91.25)	9970.90	(89.37)	<0.001
	Yes	9237.71	(8.95)	8051.19	(8.75)	1186.52	(10.63)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Ascites	No	101140.32	(98.01)	90259.80	(98.07)	10880.51	(97.52)	<0.001
	Yes	2049.24	(1.99)	1772.34	(1.93)	276.90	(2.48)	
Hepatic encephalopathy	No	101828.96	(98.68)	90855.79	(98.72)	10973.17	(98.35)	0.0011
	Yes	1360.60	(1.32)	1176.35	(1.28)	184.25	(1.65)	
Esophageal varices	No	101045.68	(97.92)	90172.71	(97.98)	10872.97	(97.45)	<0.001
	Yes	2143.88	(2.08)	1859.43	(2.02)	284.45	(2.55)	
Hapatorenal syndrome	No	103151.57	(99.96)	91999.05	(99.96)	11152.52	(99.96)	0.6781
	Yes	37.99	(0.04)	33.09	(0.04)	4.90	(0.04)	
Acute liver disease previous 1 year-Hospitalization	0-6	8798.24	(8.53)	7821.71	(8.50)	976.53	(8.75)	0.3751
	6-12	2844.01	(2.76)	2519.83	(2.74)	324.18	(2.91)	
	Never	91547.31	(88.72)	81690.59	(88.76)	9856.71	(88.34)	
Acute liver disease previous 1 year-Emergency department visit	0-6	3889.39	(3.77)	3417.90	(3.71)	471.49	(4.23)	0.0088
	6-12	1193.61	(1.16)	1049.11	(1.14)	144.50	(1.30)	
	Never	98106.56	(95.07)	87565.13	(95.15)	10541.43	(94.48)	
Myocardial infarction	No	103020.69	(99.84)	91879.94	(99.83)	11140.75	(99.85)	0.6931
	Yes	168.87	(0.16)	152.20	(0.17)	16.67	(0.15)	
Congestive heart failure	No	101989.13	(98.84)	90990.47	(98.87)	10998.67	(98.58)	0.0068
	Yes	1200.43	(1.16)	1041.67	(1.13)	158.75	(1.42)	
Peripheral vascular disease	No	102705.24	(99.53)	91606.51	(99.54)	11098.73	(99.47)	0.3538
	Yes	484.32	(0.47)	425.63	(0.46)	58.69	(0.53)	
Cerebrovascular disease	No	101367.34	(98.23)	90431.86	(98.26)	10935.47	(98.01)	0.0579
	Yes	1822.22	(1.77)	1600.28	(1.74)	221.94	(1.99)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Dementia	No	102970.02	(99.79)	91844.16	(99.80)	11125.86	(99.72)	0.0887
	Yes	219.54	(0.21)	187.98	(0.20)	31.56	(0.28)	
Chronic pulmonary disease	No	98515.65	(95.47)	87908.50	(95.52)	10607.16	(95.07)	0.0304
	Yes	4673.91	(4.53)	4123.65	(4.48)	550.26	(4.93)	
Rheumatic disease	No	102260.14	(99.10)	91208.13	(99.10)	11052.00	(99.06)	0.6016
	Yes	929.42	(0.90)	824.01	(0.90)	105.41	(0.94)	
Peptic ulcer disease	No	88528.86	(85.79)	79090.31	(85.94)	9438.55	(84.59)	<0.001
	Yes	14660.70	(14.21)	12941.83	(14.06)	1718.87	(15.41)	
Diabetes	No	93925.07	(91.02)	83843.38	(91.10)	10081.69	(90.36)	0.0095
	Yes	9264.49	(8.98)	8188.76	(8.90)	1075.73	(9.64)	
Hemiplegia or paraplegia	No	102953.60	(99.77)	91824.22	(99.77)	11129.38	(99.75)	0.5960
	Yes	235.96	(0.23)	207.92	(0.23)	28.04	(0.25)	
Renal disease	No	101549.28	(98.41)	90615.68	(98.46)	10933.60	(97.99)	<0.001
	Yes	1640.28	(1.59)	1416.46	(1.54)	223.82	(2.01)	

Supplementary Table 3. Baseline characteristics of patients treated with lamivudine compared with untreated patients (After SMRW)

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		22505.91	(100.00)	11297.91	(100.00)	11208.00	(100.00)	-
Calendar year	2004	5393.97	(23.97)	2749.97	(24.34)	2644.00	(23.59)	0.8655
	2005	4978.09	(22.12)	2509.09	(22.21)	2469.00	(22.03)	
	2006	4091.63	(18.18)	2044.63	(18.10)	2047.00	(18.26)	
	2007	4114.44	(18.28)	2050.44	(18.15)	2064.00	(18.42)	
	2008	2320.30	(10.31)	1150.30	(10.18)	1170.00	(10.44)	
	2009	635.40	(2.82)	314.40	(2.78)	321.00	(2.86)	
	2010	972.09	(4.32)	479.09	(4.24)	493.00	(4.40)	
Sex	Male	16691.50	(74.16)	8398.50	(74.34)	8293.00	(73.99)	0.5544
	Female	5814.40	(25.84)	2899.40	(25.66)	2915.00	(26.01)	
Age	Mean(SD)	40.5(6.3)		40.8(4.8)		40.2(13.2)		
	Median (min,max)	39.0(18.0, 96.0)		39.0(18.0, 96.0)		39.0(18.0, 87.0)		
Age	18-24	2460.85	(10.93)	1230.85	(10.89)	1230.00	(10.97)	0.9558
	25-34	6296.64	(27.98)	3142.64	(27.82)	3154.00	(28.14)	
	35-44	5716.65	(25.40)	2861.65	(25.33)	2855.00	(25.47)	
	45-54	4488.68	(19.94)	2259.68	(20.00)	2229.00	(19.89)	
	55-64	2374.49	(10.55)	1204.49	(10.66)	1170.00	(10.44)	
	65+	1168.61	(5.19)	598.61	(5.30)	570.00	(5.09)	
Alcoholic liver disease	No	21738.70	(96.59)	10903.70	(96.51)	10835.00	(96.67)	0.5051
	Yes	767.21	(3.41)	394.21	(3.49)	373.00	(3.33)	
Cirrhosis of liver without mention of alcohol	No	18489.37	(82.15)	9186.37	(81.31)	9303.00	(83.00)	<0.001
	Yes	4016.54	(17.85)	2111.54	(18.69)	1905.00	(17.00)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Ascites	No	21550.54	(95.76)	10792.54	(95.53)	10758.00	(95.99)	0.0883
	Yes	955.37	(4.24)	505.37	(4.47)	450.00	(4.01)	
Hepatic encephalopathy	No	21993.18	(97.72)	11032.18	(97.65)	10961.00	(97.80)	0.4560
	Yes	512.73	(2.28)	265.73	(2.35)	247.00	(2.20)	
Esophageal varices	No	21648.84	(96.19)	10851.84	(96.05)	10797.00	(96.33)	0.2704
	Yes	857.07	(3.81)	446.07	(3.95)	411.00	(3.67)	
Hapatorenal syndrome	No	22497.78	(99.96)	11293.78	(99.96)	11204.00	(99.96)	0.9742
	Yes	8.12	(0.04)	4.12	(0.04)	4.00	(0.04)	
Acute liver disease previous 1 year-Hospitalization	0-6	5032.10	(22.36)	2574.10	(22.78)	2458.00	(21.93)	0.3002
	6-12	868.97	(3.86)	436.97	(3.87)	432.00	(3.85)	
	Never	16604.83	(73.78)	8286.83	(73.35)	8318.00	(74.21)	
Acute liver disease previous 1 year-Emergency department visit	0-6	2310.51	(10.27)	1214.51	(10.75)	1096.00	(9.78)	0.0487
	6-12	397.98	(1.77)	203.98	(1.81)	194.00	(1.73)	
	Never	19797.42	(87.97)	9879.42	(87.44)	9918.00	(88.49)	
Myocardial infarction	No	22456.16	(99.78)	11272.16	(99.77)	11184.00	(99.79)	0.8258
	Yes	49.75	(0.22)	25.75	(0.23)	24.00	(0.21)	
Congestive heart failure	No	22243.27	(98.83)	11161.27	(98.79)	11082.00	(98.88)	0.5515
	Yes	262.64	(1.17)	136.64	(1.21)	126.00	(1.12)	
Peripheral vascular disease	No	22413.40	(99.59)	11250.40	(99.58)	11163.00	(99.60)	0.8234
	Yes	92.51	(0.41)	47.51	(0.42)	45.00	(0.40)	
Cerebrovascular disease	No	22166.57	(98.49)	11124.57	(98.47)	11042.00	(98.52)	0.7436
	Yes	339.34	(1.51)	173.34	(1.53)	166.00	(1.48)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Dementia	No	22463.02	(99.81)	11276.02	(99.81)	11187.00	(99.81)	0.9124
	Yes	42.89	(0.19)	21.89	(0.19)	21.00	(0.19)	
Chronic pulmonary disease	No	21558.63	(95.79)	10813.63	(95.71)	10745.00	(95.87)	0.5615
	Yes	947.28	(4.21)	484.28	(4.29)	463.00	(4.13)	
Rheumatic disease	No	22239.46	(98.82)	11164.46	(98.82)	11075.00	(98.81)	0.9697
	Yes	266.45	(1.18)	133.45	(1.18)	133.00	(1.19)	
Peptic ulcer disease	No	18093.60	(80.39)	9030.60	(79.93)	9063.00	(80.86)	0.0788
	Yes	4412.31	(19.61)	2267.31	(20.07)	2145.00	(19.14)	
Diabetes	No	20487.02	(91.03)	10265.02	(90.86)	10222.00	(91.20)	0.3651
	Yes	2018.89	(8.97)	1032.89	(9.14)	986.00	(8.80)	
Hemiplegia or paraplegia	No	22459.65	(99.79)	11274.65	(99.79)	11185.00	(99.79)	0.9912
	Yes	46.26	(0.21)	23.26	(0.21)	23.00	(0.21)	
Renal disease	No	21988.80	(97.70)	11023.80	(97.57)	10965.00	(97.83)	0.1963
	Yes	517.11	(2.30)	274.11	(2.43)	243.00	(2.17)	

Supplementary Table 4. Baseline characteristics of patients treated with lamivudine compared with untreated patients (After PS matching)

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		12296	(100.0)	6148	(100.0)	6148	(100.0)	-
FECF-Incidence(Person Years)		52385.6		25041.5		27344.1		
AT-Incidence(Person Years)		48471.3		25041.5		23429.8		
FECF-Mortality(Person Months)		626909.5		299676.4		327233.1		
AT-Mortality(Person Months)		580066.3		299676.4		280389.9		
FECF-Median follow-up time of Incidence(months)	Mean(SD)	51.0(22.8)		48.7(24.1)		53.2(21.2)		<0.0001
	Median (Q1,Q3)	54.5(36.3, 70.1)		52.0(33.2, 69.1)		56.6(39.0, 71.0)		
	Median (min,max)	54.5(0.0, 83.8)		52.0(0.0, 83.8)		56.6(0.0, 83.8)		
AT-Median follow-up time of Incidence(months)	Mean(SD)	47.2(23.8)		48.7(24.1)		45.6(23.4)		<0.0001
	Median (Q1,Q3)	48.9(30.1, 67.8)		52.0(33.2, 69.1)		46.4(26.6, 66.1)		
	Median (min,max)	48.9(0.0, 83.8)		52.0(0.0, 83.8)		46.4(0.0, 83.8)		
FECF-Mortality(Person Year)		53846.5		26185.2		27661.3		
AT-Mortality(Person Year)		49846.5		26185.2		23661.3		
FECF-Mortality(Person Months)		644392.9		313364.1		331028.8		
AT-Mortality(Person Months)		596523.4		313364.1		283159.3		
FECF-Median follow-up time of Mortality(months)	Mean(SD)	52.4(21.6)		51.0(22.3)		53.8(20.8)		<0.0001
	Median (Q1,Q3)	55.6(37.9, 70.7)		54.0(36.1, 69.9)		57.0(39.8, 71.2)		
	Median (min,max)	55.6(0.0, 83.8)		54.0(0.0, 83.8)		57.0(0.0, 83.8)		
AT-Median follow-up time of Mortality(months)	Mean(SD)	48.5(22.9)		51.0(22.3)		46.1(23.3)		<0.0001
	Median (Q1,Q3)	50.1(32.0, 68.3)		54.0(36.1, 69.9)		46.7(27.4, 66.6)		
	Median (min,max)	50.1(0.0, 83.8)		54.0(0.0, 83.8)		46.7(0.0, 83.8)		
Calendar year	2004	3000	(24.4)	1500	(24.4)	1500	(24.4)	-

		Total		Untreated		LAM	
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	2005	2776	(22.6)	1388	(22.6)	1388	(22.6)	
	2006	2186	(17.8)	1093	(17.8)	1093	(17.8)	
	2007	2228	(18.1)	1114	(18.1)	1114	(18.1)	
	2008	1280	(10.4)	640	(10.4)	640	(10.4)	
	2009	352	(2.9)	176	(2.9)	176	(2.9)	
	2010	474	(3.9)	237	(3.9)	237	(3.9)	
Sex	Male	9004	(73.2)	4502	(73.2)	4502	(73.2)	-
	Female	3292	(26.8)	1646	(26.8)	1646	(26.8)	
Age	Mean(SD)	37.2(12.5)		37.4(12.6)		37.0(12.5)		0.0500
	Median (Q1,Q3)	35.0(27.0, 44.0)		35.0(28.0, 44.0)		35.0(27.0, 44.0)		
	Median (min,max)	35.0(18.0, 95.0)		35.0(18.0, 95.0)		35.0(18.0, 84.0)		
Age	Mean(SD)	37.2(12.5)		37.4(12.6)		37.0(12.5)		<0.001
	Median (min,max)	35.0(18.0, 95.0)		35.0(18.0, 95.0)		35.0(18.0, 84.0)		
Age	18-24	1888	(15.4)	944	(15.4)	944	(15.4)	-
	25-34	4248	(34.5)	2124	(34.5)	2124	(34.5)	
	35-44	3118	(25.4)	1559	(25.4)	1559	(25.4)	
	45-54	1728	(14.1)	864	(14.1)	864	(14.1)	
	55-64	910	(7.4)	455	(7.4)	455	(7.4)	
	65+	404	(3.3)	202	(3.3)	202	(3.3)	
Alcoholic liver disease	No	12155	(98.9)	6066	(98.7)	6089	(99.0)	0.0350
	Yes	141	(1.1)	82	(1.3)	59	(1.0)	
Cirrhosis of liver without mention of alcohol	No	11597	(94.3)	5813	(94.6)	5784	(94.1)	0.0847
	Yes	699	(5.7)	335	(5.4)	364	(5.9)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Ascites	No	12163	(98.9)	6087	(99.0)	6076	(98.8)	0.3133
	Yes	133	(1.1)	61	(1.0)	72	(1.2)	
Hepatic encephalopathy	No	12198	(99.2)	6100	(99.2)	6098	(99.2)	0.8399
	Yes	98	(0.8)	48	(0.8)	50	(0.8)	
Esophageal varices	No	12124	(98.6)	6063	(98.6)	6061	(98.6)	0.8711
	Yes	172	(1.4)	85	(1.4)	87	(1.4)	
Hapatorenal syndrome	No			合併為 6148		6148	(100.0)	0.3173
	Yes							
Acute liver disease previous 1 year-Hospitalization	0-6	543	(4.4)	284	(4.6)	259	(4.2)	0.0215
	6-12	192	(1.6)	104	(1.7)	88	(1.4)	
	Never	11561	(94.0)	5760	(93.7)	5801	(94.4)	
Acute liver disease previous 1 year-Emergency department visit	0-6	193	(1.6)	97	(1.6)	96	(1.6)	0.9909
	6-12	91	(0.7)	45	(0.7)	46	(0.7)	
	Never	12012	(97.7)	6006	(97.7)	6006	(97.7)	
Myocardial infarction	No	12286	(99.9)	6145	(100.0)	6141	(99.9)	0.2059
	Yes	10	(0.1)	3	(0.0)	7	(0.1)	
Congestive heart failure	No	12235	(99.5)	6116	(99.5)	6119	(99.5)	0.6744
	Yes	61	(0.5)	32	(0.5)	29	(0.5)	
Peripheral vascular disease	No	12266	(99.8)	6135	(99.8)	6131	(99.7)	0.4652
	Yes	30	(0.2)	13	(0.2)	17	(0.3)	
Cerebrovascular disease	No	12225	(99.4)	6106	(99.3)	6119	(99.5)	0.1069
	Yes	71	(0.6)	42	(0.7)	29	(0.5)	

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Dementia	No	12286	(99.9)	6143	(99.9)	6143	(99.9)	1.0000
	Yes	10	(0.1)	5	(0.1)	5	(0.1)	
Chronic pulmonary disease	No	12048	(98.0)	6025	(98.0)	6023	(98.0)	0.8808
	Yes	248	(2.0)	123	(2.0)	125	(2.0)	
Rheumatic disease	No	12258	(99.7)	6129	(99.7)	6129	(99.7)	1.0000
	Yes	38	(0.3)	19	(0.3)	19	(0.3)	
Peptic ulcer disease	No	11204	(91.1)	5592	(91.0)	5612	(91.3)	0.1948
	Yes	1092	(8.9)	556	(9.0)	536	(8.7)	
Diabetes	No	11782	(95.8)	5888	(95.8)	5894	(95.9)	0.7021
	Yes	514	(4.2)	260	(4.2)	254	(4.1)	
Hemiplegia or paraplegia	No			6143	(99.9)	合併為 6148		0.2568
	Yes			5	(0.1)			
Renal disease	No	12143	(98.8)	6089	(99.0)	6054	(98.5)	0.0024
	Yes	153	(1.2)	59	(1.0)	94	(1.5)	
FECF - HCC incidence	No	11617	(94.5)	5633	(91.6)	5984	(97.3)	<0.001
	Yes	679	(5.5)	515	(8.4)	164	(2.7)	
AT - HCC incidence	No	11646	(94.7)	5633	(91.6)	6013	(97.8)	<0.001
	Yes	650	(5.3)	515	(8.4)	135	(2.2)	
FECF - All-cause mortality	No	11547	(93.9)	5646	(91.8)	5901	(96.0)	<0.001
	Yes	749	(6.1)	502	(8.2)	247	(4.0)	
AT - All-cause mortality	No	11584	(94.2)	5646	(91.8)	5938	(96.6)	<0.001
	Yes	712	(5.8)	502	(8.2)	210	(3.4)	
FECF - Liver-related mortality	No	11835	(96.3)	5838	(95.0)	5997	(97.5)	<0.001

		Total		Untreated		LAM		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	461	(3.7)	310	(5.0)	151	(2.5)	
AT - Liver-related mortality	No	11862	(96.5)	5838	(95.0)	6024	(98.0)	<0.001
	Yes	434	(3.5)	310	(5.0)	124	(2.0)	

Supplementary Table 5. Baseline characteristics of patients treated with interferon or peg-interferon compared with untreated patients (Before covariates adjustment)

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		25919	(100.0)	23214	(100.0)	2705	(100.0)	-
FECF-Incidence(Person Years)		62577.5		54932.8		7644.7		
AT-Incidence(Person Years)		62039.9		54932.8		7107.1		
FECF-Incidence(Person Months)		748878.4		657392.3		91486.1		
AT-Incidence(Person Months)		742444.5		657392.3		85052.1		
FECF-Median follow-up time of incidence(months)	Mean(SD)	28.9(19.4)		28.3(19.2)		33.8(20.5)		<0.0001
	Median (Q1,Q3)	26.3(12.2, 44.6)		25.7(12.0, 44.0)		32.8(15.7, 51.2)		
	Median (min,max)	26.3(0.0, 83.8)		25.7(0.0, 83.3)		32.8(0.0, 83.8)		
AT-Median follow-up time of incidence(months)	Mean(SD)	28.6(19.3)		28.3(19.2)		31.4(20.4)		<0.0001
	Median (Q1,Q3)	26.1(12.1, 44.3)		25.7(12.0, 44.0)		29.2(13.6, 48.0)		
	Median (min,max)	26.1(0.0, 83.8)		25.7(0.0, 83.3)		29.2(0.0, 83.8)		
FECF-Mortality(Person Years)		65268.3		57554.9		7713.4		
AT-Mortality(Person Years)		64720.6		57554.9		7165.7		
FECF-Mortality(Person Months)		781080.1		688772.0		92308.1		
AT-Mortality(Person Months)		774525.7		688772.0		85753.7		
FECF-Median follow-up time of Mortality(months)	Mean(SD)	30.1(19.4)		29.7(19.2)		34.1(20.5)		<0.0001
	Median (Q1,Q3)	28.1(13.1, 46.3)		27.4(12.9, 45.4)		33.2(16.1, 51.9)		
	Median (min,max)	28.1(0.0, 83.8)		27.4(0.0, 83.8)		33.2(0.0, 83.8)		
AT-Median follow-up time of Mortality(months)	Mean(SD)	29.9(19.4)		29.7(19.2)		31.7(20.4)		<0.0001
	Median (Q1,Q3)	27.7(13.0, 45.9)		27.4(12.9, 45.4)		29.6(14.0, 48.0)		
	Median (min,max)	27.7(0.0, 83.8)		27.4(0.0, 83.8)		29.6(0.0, 83.8)		

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Duration of interferon therapy(Months)	Mean(SD)	6.6(3.4)				6.6(3.4)		
	Median (Q1,Q3)	5.6(5.0, 9.4)				5.6(5.0, 9.4)		
	Median (min,max)	5.6(0.0, 23.6)				5.6(0.0, 23.6)		
Switching	No	25459	(98.2)	23214	(100.0)	2245	(83.0)	<0.001
	Yes	460	(1.8)			460	(17.0)	
Calendar year	2004	762	(2.9)	653	(2.8)	109	(4.0)	<0.001
	2005	1469	(5.7)	1284	(5.5)	185	(6.8)	
	2006	4588	(17.7)	4066	(17.5)	522	(19.3)	
	2007	4150	(16.0)	3710	(16.0)	440	(16.3)	
	2008	4804	(18.5)	4314	(18.6)	490	(18.1)	
	2009	5207	(20.1)	4710	(20.3)	497	(18.4)	
	2010	4939	(19.1)	4477	(19.3)	462	(17.1)	
Sex	Male	19467	(75.1)	17378	(74.9)	2089	(77.2)	0.0070
	Female	6452	(24.9)	5836	(25.1)	616	(22.8)	
Age	Mean(SD)	36.4(10.7)		36.4(10.7)		36.4(10.4)		0.7370
	Median (Q1,Q3)	34.0(28.0, 43.0)		34.0(28.0, 43.0)		35.0(28.0, 43.0)		
	Median (min,max)	34.0(18.0, 86.0)		34.0(18.0, 86.0)		35.0(18.0, 78.0)		
Age	18-24	3402	(13.1)	3078	(13.3)	324	(12.0)	0.1049
	25-34	9736	(37.6)	8751	(37.7)	985	(36.4)	
	35-44	7058	(27.2)	6270	(27.0)	788	(29.1)	
	45-54	4239	(16.4)	3780	(16.3)	459	(17.0)	
	55-64	1305	(5.0)	1173	(5.1)	132	(4.9)	
	65+	179	(0.7)	162	(0.7)	17	(0.6)	

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Alcoholic liver disease	No	25399	(98.0)	22709	(97.8)	2690	(99.4)	<0.001
	Yes	520	(2.0)	505	(2.2)	15	(0.6)	
Cirrhosis of liver without mention of alcohol	No	24815	(95.7)	22236	(95.8)	2579	(95.3)	0.2780
	Yes	1104	(4.3)	978	(4.2)	126	(4.7)	
Ascites	No	25919	(100.0)	23214	(100.0)	2705	(100.0)	-
Hepatic encephalopathy	No	25919	(100.0)	23214	(100.0)	2705	(100.0)	-
Esophageal varices	No	25919	(100.0)	23214	(100.0)	2705	(100.0)	-
Hapatorenal syndrome	No	25919	(100.0)	23214	(100.0)	2705	(100.0)	-
Acute liver disease previous 1 year-Hospitalization	0-6	1267	(4.9)	898	(3.9)	369	(13.6)	<0.001
	6-12	586	(2.3)	509	(2.2)	77	(2.8)	
	Never	24066	(92.9)	21807	(93.9)	2259	(83.5)	
Acute liver disease previous 1 year-Emergency department visit	0-6	384	(1.5)	333	(1.4)	51	(1.9)	0.1098
	6-12	181	(0.7)	158	(0.7)	23	(0.9)	
	Never	25354	(97.8)	22723	(97.9)	2631	(97.3)	
Myocardial infarction	No	25885	(99.9)	23184	(99.9)	2701	(99.9)	0.7999
	Yes	34	(0.1)	30	(0.1)	4	(0.1)	
Congestive heart failure	No	25790	(99.5)	23091	(99.5)	2699	(99.8)	0.0312
	Yes	129	(0.5)	123	(0.5)	6	(0.2)	
Peripheral vascular disease	No	25851	(99.7)	23151	(99.7)	2700	(99.8)	0.4050
	Yes	68	(0.3)	63	(0.3)	5	(0.2)	
Cerebrovascular disease	No	25679	(99.1)	22992	(99.0)	2687	(99.3)	0.1350
	Yes	240	(0.9)	222	(1.0)	18	(0.7)	

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Dementia	No	25908	(100.0)	23203	(100.0)	2705	(100.0)	0.2575
	Yes	11	(0.0)	11	(0.0)			
Chronic pulmonary disease	No	25074	(96.7)	22446	(96.7)	2628	(97.2)	0.2006
	Yes	845	(3.3)	768	(3.3)	77	(2.8)	
Rheumatic disease	No	25753	(99.4)	23065	(99.4)	2688	(99.4)	0.9342
	Yes	166	(0.6)	149	(0.6)	17	(0.6)	
Peptic ulcer disease	No	23393	(90.3)	21018	(90.5)	2375	(87.8)	<0.001
	Yes	2526	(9.7)	2196	(9.5)	330	(12.2)	
Diabetes	No	24099	(93.0)	21561	(92.9)	2538	(93.8)	0.0681
	Yes	1820	(7.0)	1653	(7.1)	167	(6.2)	
Hemiplegia or paraplegia	No	合併為 25919		23171	(99.8)	合併為 2705		0.0763
	Yes			43	(0.2)			
Renal disease	No	25671	(99.0)	22989	(99.0)	2682	(99.1)	0.5475
	Yes	248	(1.0)	225	(1.0)	23	(0.9)	
FECF - HCC incidence	No	24565	(94.8)	21904	(94.4)	2661	(98.4)	<0.001
	Yes	1354	(5.2)	1310	(5.6)	44	(1.6)	
AT - HCC incidence	No	24570	(94.8)	21904	(94.4)	2666	(98.6)	<0.001
	Yes	1349	(5.2)	1310	(5.6)	39	(1.4)	
FECF - All-cause mortality	No	24657	(95.1)	21973	(94.7)	2684	(99.2)	<0.001
	Yes	1262	(4.9)	1241	(5.3)	21	(0.8)	
AT - All-cause mortality	No	24663	(95.2)	21973	(94.7)	2690	(99.4)	<0.001
	Yes	1256	(4.8)	1241	(5.3)	15	(0.6)	
FECF - Liver-related mortality	No	25258	(97.4)	22568	(97.2)	2690	(99.4)	<0.001

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	661	(2.6)	646	(2.8)	15	(0.6)	
AT - Liver-related mortality	No	25263	(97.5)	22568	(97.2)	2695	(99.6)	<0.001
	Yes	656	(2.5)	646	(2.8)	10	(0.4)	

Supplementary Table 6. Baseline characteristics of patients treated with interferon or peg-interferon compared with untreated patients (After IPTW)

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		25996.96	(100.00)	23207.95	(100.00)	2789.01	(100.00)	-
Calendar year	2004	767.07	(2.95)	685.88	(2.96)	81.19	(2.91)	0.0750
	2005	1453.90	(5.59)	1310.28	(5.65)	143.63	(5.15)	
	2006	4575.95	(17.60)	4104.17	(17.68)	471.77	(16.92)	
	2007	4143.28	(15.94)	3717.17	(16.02)	426.11	(15.28)	
	2008	4788.87	(18.42)	4296.11	(18.51)	492.76	(17.67)	
	2009	5235.44	(20.14)	4661.53	(20.09)	573.92	(20.58)	
	2010	5032.45	(19.36)	4432.82	(19.10)	599.63	(21.50)	
Sex	Male	19550.22	(75.20)	17435.16	(75.13)	2115.05	(75.84)	0.4124
	Female	6446.75	(24.80)	5772.79	(24.87)	673.96	(24.16)	
Age	Mean(SD)	36.4(10.7)		36.4(10.7)		36.2(10.8)		
	Median (min,max)	34.0(18.0, 86.0)		34.0(18.0, 86.0)		34.0(18.0, 78.0)		
Age	18-24	3390.92	(13.04)	3043.92	(13.12)	347.00	(12.44)	0.4922
	25-34	9787.56	(37.65)	8720.21	(37.57)	1067.35	(38.27)	
	35-44	7046.84	(27.11)	6319.33	(27.23)	727.51	(26.09)	
	45-54	4282.53	(16.47)	3794.61	(16.35)	487.92	(17.49)	
	55-64	1307.72	(5.03)	1168.66	(5.04)	139.06	(4.99)	
	65+	181.39	(0.70)	161.22	(0.69)	20.16	(0.72)	
Alcoholic liver disease	No	25398.93	(97.70)	22741.90	(97.99)	2657.03	(95.27)	<0.001
	Yes	598.03	(2.30)	466.05	(2.01)	131.98	(4.73)	
Cirrhosis of liver without mention of alcohol	No	24870.27	(95.67)	22211.23	(95.71)	2659.04	(95.34)	0.3707

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	1126.70	(4.33)	996.73	(4.29)	129.97	(4.66)	
Ascites	No	25996.96	(100.00)	23207.95	(100.00)	2789.01	(100.00)	-
Hepatic encephalopathy	No	25996.96	(100.00)	23207.95	(100.00)	2789.01	(100.00)	-
Esophageal varices	No	25996.96	(100.00)	23207.95	(100.00)	2789.01	(100.00)	-
Hapatorenal syndrome	No	25996.96	(100.00)	23207.95	(100.00)	2789.01	(100.00)	-
Acute liver disease previous 1 year-Hospitalization	0-6	1242.89	(4.78)	1128.05	(4.86)	114.84	(4.12)	0.1907
	6-12	584.17	(2.25)	525.08	(2.26)	59.09	(2.12)	
	Never	24169.90	(92.97)	21554.83	(92.88)	2615.08	(93.76)	
Acute liver disease previous 1 year-Emergency department visit	0-6	391.03	(1.50)	347.08	(1.50)	43.95	(1.58)	0.7451
	6-12	187.50	(0.72)	164.48	(0.71)	23.03	(0.83)	
	Never	25418.43	(97.77)	22696.40	(97.80)	2722.03	(97.60)	
Myocardial infarction	No	25962.08	(99.87)	23177.40	(99.87)	2784.68	(99.84)	0.7487
	Yes	34.88	(0.13)	30.55	(0.13)	4.33	(0.16)	
Congestive heart failure	No	25865.09	(99.49)	23092.19	(99.50)	2772.90	(99.42)	0.5799
	Yes	131.87	(0.51)	115.76	(0.50)	16.11	(0.58)	
Peripheral vascular disease	No	25928.01	(99.73)	23146.78	(99.74)	2781.23	(99.72)	0.8810
	Yes	68.96	(0.27)	61.17	(0.26)	7.78	(0.28)	
Cerebrovascular disease	No	25738.92	(99.01)	22992.05	(99.07)	2746.87	(98.49)	0.0035
	Yes	258.05	(0.99)	215.90	(0.93)	42.14	(1.51)	
Dementia	No	25987.11	(99.96)	23198.10	(99.96)	2789.01	(100.00)	0.2765
	Yes	9.85	(0.04)	9.85	(0.04)			
Chronic pulmonary disease	No	25144.09	(96.72)	22448.72	(96.73)	2695.37	(96.64)	0.8098

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	852.87	(3.28)	759.23	(3.27)	93.64	(3.36)	
Rheumatic disease	No	25831.64	(99.36)	23059.38	(99.36)	2772.26	(99.40)	0.8039
	Yes	165.33	(0.64)	148.58	(0.64)	16.75	(0.60)	
Peptic ulcer disease	No	23427.84	(90.12)	20932.54	(90.20)	2495.30	(89.47)	0.2243
	Yes	2569.13	(9.88)	2275.41	(9.80)	293.72	(10.53)	
Diabetes	No	24122.10	(92.79)	21571.32	(92.95)	2550.78	(91.46)	0.0041
	Yes	1874.86	(7.21)	1636.63	(7.05)	238.23	(8.54)	
Hemiplegia or paraplegia	No	25953.20	(99.83)	23168.53	(99.83)	2784.68	(99.84)	0.8599
	Yes	43.76	(0.17)	39.43	(0.17)	4.33	(0.16)	
Renal disease	No	25742.72	(99.02)	22984.47	(99.04)	2758.25	(98.90)	0.4777
	Yes	254.25	(0.98)	223.49	(0.96)	30.76	(1.10)	

Supplementary Table 7. Baseline characteristics of patients treated with interferon or peg-interferon compared with untreated patients (After SMRW)

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		5403.25	(100.00)	2698.25	(100.00)	2705.00	(100.00)	-
Calendar year	2004	221.80	(4.10)	112.80	(4.18)	109.00	(4.03)	0.9991
	2005	363.95	(6.74)	178.95	(6.63)	185.00	(6.84)	
	2006	1038.41	(19.22)	516.41	(19.14)	522.00	(19.30)	
	2007	880.31	(16.29)	440.31	(16.32)	440.00	(16.27)	
	2008	972.72	(18.00)	482.72	(17.89)	490.00	(18.11)	
	2009	991.71	(18.35)	494.71	(18.33)	497.00	(18.37)	
	2010	934.35	(17.29)	472.35	(17.51)	462.00	(17.08)	
Sex	Male	4177.79	(77.32)	2088.79	(77.41)	2089.00	(77.23)	0.8707
	Female	1225.46	(22.68)	609.46	(22.59)	616.00	(22.77)	
Age	Mean(SD)	36.6(4.8)		36.8(3.6)		36.4(10.4)		
	Median (min,max)	35.0(18.0, 86.0)		35.0(18.0, 86.0)		35.0(18.0, 78.0)		
Age	18-24	644.61	(11.93)	320.61	(11.88)	324.00	(11.98)	1.0000
	25-34	1970.32	(36.47)	985.32	(36.52)	985.00	(36.41)	
	35-44	1573.68	(29.12)	785.68	(29.12)	788.00	(29.13)	
	45-54	915.78	(16.95)	456.78	(16.93)	459.00	(16.97)	
	55-64	263.84	(4.88)	131.84	(4.89)	132.00	(4.88)	
	65+	35.01	(0.65)	18.01	(0.67)	17.00	(0.63)	
Alcoholic liver disease	No	5372.89	(99.44)	2682.89	(99.43)	2690.00	(99.45)	0.9423
	Yes	30.36	(0.56)	15.36	(0.57)	15.00	(0.55)	
Cirrhosis of liver without mention of alcohol	No	5142.38	(95.17)	2563.38	(95.00)	2579.00	(95.34)	0.5595

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	260.87	(4.83)	134.87	(5.00)	126.00	(4.66)	
Ascites	No	5403.25	(100.00)	2698.25	(100.00)	2705.00	(100.00)	-
Hepatic encephalopathy	No	5403.25	(100.00)	2698.25	(100.00)	2705.00	(100.00)	-
Esophageal varices	No	5403.25	(100.00)	2698.25	(100.00)	2705.00	(100.00)	-
Hapatorenal syndrome	No	5403.25	(100.00)	2698.25	(100.00)	2705.00	(100.00)	-
Acute liver disease previous 1 year-Hospitalization	0-6	730.49	(13.52)	361.49	(13.40)	369.00	(13.64)	0.9660
	6-12	154.26	(2.86)	77.26	(2.86)	77.00	(2.85)	
	Never	4518.49	(83.63)	2259.49	(83.74)	2259.00	(83.51)	
Acute liver disease previous 1 year-Emergency department visit	0-6	105.52	(1.95)	54.52	(2.02)	51.00	(1.89)	0.8675
	6-12	48.64	(0.90)	25.64	(0.95)	23.00	(0.85)	
	Never	5249.09	(97.15)	2618.09	(97.03)	2631.00	(97.26)	
Myocardial infarction	No	5395.14	(99.85)	2694.14	(99.85)	2701.00	(99.85)	0.9657
	Yes	8.11	(0.15)	4.11	(0.15)	4.00	(0.15)	
Congestive heart failure	No	5391.00	(99.77)	2692.00	(99.77)	2699.00	(99.78)	0.9386
	Yes	12.25	(0.23)	6.25	(0.23)	6.00	(0.22)	
Peripheral vascular disease	No	5392.95	(99.81)	2692.95	(99.80)	2700.00	(99.82)	0.9217
	Yes	10.30	(0.19)	5.30	(0.20)	5.00	(0.18)	
Cerebrovascular disease	No	5366.19	(99.31)	2679.19	(99.29)	2687.00	(99.33)	0.8552
	Yes	37.06	(0.69)	19.06	(0.71)	18.00	(0.67)	
Dementia	No	5403.25	(100.00)	2698.25	(100.00)	2705.00	(100.00)	0.9929
	Yes	0.00	(0.00)	0.00	(0.00)			
Chronic pulmonary disease	No	5246.54	(97.10)	2618.54	(97.05)	2628.00	(97.15)	0.8141

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	156.70	(2.90)	79.70	(2.95)	77.00	(2.85)	
Rheumatic disease	No	5369.36	(99.37)	2681.36	(99.37)	2688.00	(99.37)	0.9905
	Yes	33.89	(0.63)	16.89	(0.63)	17.00	(0.63)	
Peptic ulcer disease	No	4728.70	(87.52)	2353.70	(87.23)	2375.00	(87.80)	0.5263
	Yes	674.55	(12.48)	344.55	(12.77)	330.00	(12.20)	
Diabetes	No	5061.91	(93.68)	2523.91	(93.54)	2538.00	(93.83)	0.6640
	Yes	341.34	(6.32)	174.34	(6.46)	167.00	(6.17)	
Renal disease	No	5355.72	(99.12)	2673.72	(99.09)	2682.00	(99.15)	0.8172
	Yes	47.53	(0.88)	24.53	(0.91)	23.00	(0.85)	

Supplementary Table 8. Baseline characteristics of patients treated with interferon or peg-interferon compared with untreated patients (After PS matching)

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
Total		3768	(100.0)	1884	(100.0)	1884	(100.0)	-
FECF-Incidence(Person Years)		9366.4		4279.4		5087.0		
AT-Incidence(Person Years)		9061.7		4279.4		4782.2		
FECF-Mortality(Person Months)		112090.0		51213.0		60877.0		
AT-Mortality(Person Months)		108442.9		51213.0		57229.9		
FECF-Median follow-up time of Incidence(months)	Mean(SD)	29.7(20.1)		27.2(19.4)		32.3(20.4)		<0.0001
	Median (Q1,Q3)	27.8(12.2, 46.0)		24.4(10.5, 43.0)		31.2(13.5, 48.9)		
	Median (min,max)	27.8(0.0, 83.8)		24.4(0.0, 82.8)		31.2(0.0, 83.8)		
AT-Median follow-up time of Incidence(months)	Mean(SD)	28.8(19.9)		27.2(19.4)		30.4(20.3)		<0.0001
	Median (Q1,Q3)	26.3(11.6, 44.4)		24.4(10.5, 43.0)		28.1(12.7, 46.6)		
	Median (min,max)	26.3(0.0, 83.8)		24.4(0.0, 82.8)		28.1(0.0, 83.8)		
FECF-Mortality(Person Year)		9796.9		4668.1		5128.7		
AT-Mortality(Person Year)		9487.4		4668.1		4819.3		
FECF-Mortality(Person Months)		117241.4		55864.7		61376.7		
AT-Mortality(Person Months)		113537.9		55864.7		57673.2		
FECF-Median follow-up time of Mortality(months)	Mean(SD)	31.1(20.2)		29.7(19.8)		32.6(20.5)		<0.0001
	Median (Q1,Q3)	29.5(13.1, 47.2)		27.4(12.3, 45.2)		31.6(13.7, 48.9)		
	Median (min,max)	29.5(0.0, 83.8)		27.4(0.0, 83.8)		31.6(0.0, 83.8)		
AT-Median follow-up time of Mortality(months)	Mean(SD)	30.1(20.1)		29.7(19.8)		30.6(20.4)		0.2027
	Median (Q1,Q3)	28.0(12.5, 46.0)		27.4(12.3, 45.2)		28.4(12.9, 46.9)		
	Median (min,max)	28.0(0.0, 83.8)		27.4(0.0, 83.8)		28.4(0.0, 83.8)		

		Total			Untreated			IFN			
Variable	**Group**	**n**		**(%)**	**n**		**(%)**	**n**		**(%)**	**P value**
Calendar year	2004	134		(3.6)	67		(3.6)	67		(3.6)	-
	2005	222		(5.9)	111		(5.9)	111		(5.9)	
	2006	664		(17.6)	332		(17.6)	332		(17.6)	
	2007	618		(16.4)	309		(16.4)	309		(16.4)	
	2008	668		(17.7)	334		(17.7)	334		(17.7)	
	2009	722		(19.2)	361		(19.2)	361		(19.2)	
	2010	740		(19.6)	370		(19.6)	370		(19.6)	
Sex	Male	2854		(75.7)	1427		(75.7)	1427		(75.7)	-
	Female	914		(24.3)	457		(24.3)	457		(24.3)	
Age	Mean(SD)	35.7(	10.3)		36.0(	10.4)		35.5(	10.3)		0.1461
	Median (Q1,Q3)	34.0(	28.0,	42.0)	34.0(	28.0,	43.0)	34.0(	28.0,	42.0)	
	Median (min,max)	34.0(	18.0,	78.0)	34.0(	18.0,	77.0)	34.0(	18.0,	78.0)	
Age	Mean(SD)	35.7(	10.3)		36.0(	10.4)		35.5(	10.3)		<0.001
	Median (min,max)	34.0(	18.0,	78.0)	34.0(	18.0,	77.0)	34.0(	18.0,	78.0)	
Age	18-24	508		(13.5)	254		(13.5)	254		(13.5)	-
	25-34	1462		(38.8)	731		(38.8)	731		(38.8)	
	35-44	1028		(27.3)	514		(27.3)	514		(27.3)	
	45-54	594		(15.8)	297		(15.8)	297		(15.8)	
	55-64	148		(3.9)	74		(3.9)	74		(3.9)	
	65+	28		(0.7)	14		(0.7)	14		(0.7)	
Alcoholic liver disease	No				合併為 1884			1884		(100.0)	0.3173
	Yes										
Cirrhosis of liver without mention of alcohol	No	3688		(97.9)	1843		(97.8)	1845		(97.9)	0.7815

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	80	(2.1)	41	(2.2)	39	(2.1)	
Ascites	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Hepatic encephalopathy	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Esophageal varices	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Hapatorenal syndrome	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Acute liver disease previous 1 year-Hospitalization	0-6	56	(1.5)	29	(1.5)	27	(1.4)	0.2231
	6-12	18	(0.5)	11	(0.6)	7	(0.4)	
	Never	3694	(98.0)	1844	(97.9)	1850	(98.2)	
Acute liver disease previous 1 year-Emergency department visit	0-6	11	(0.3)	6	(0.3)	5	(0.3)	0.9460
	6-12	12	(0.3)	6	(0.3)	6	(0.3)	
	Never	3745	(99.4)	1872	(99.4)	1873	(99.4)	
Myocardial infarction	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Congestive heart failure	No			合併為 1884		合併為 1884		0.5637
	Yes							
Peripheral vascular disease	No			1884	(100.0)	合併為 1884		0.3173
	Yes							
Cerebrovascular disease	No	3756	(99.7)	1879	(99.7)	1877	(99.6)	0.5637
	Yes	12	(0.3)	5	(0.3)	7	(0.4)	
Dementia	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Chronic pulmonary disease	No	3713	(98.5)	1863	(98.9)	1850	(98.2)	0.0326
	Yes	55	(1.5)	21	(1.1)	34	(1.8)	
Rheumatic disease	No	3759	(99.8)	1879	(99.7)	1880	(99.8)	0.7055

		Total		Untreated		IFN		
Variable	**Group**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**P value**
	Yes	9	(0.2)	5	(0.3)	4	(0.2)	
Peptic ulcer disease	No	3550	(94.2)	1784	(94.7)	1766	(93.7)	0.0126
	Yes	218	(5.8)	100	(5.3)	118	(6.3)	
Diabetes	No	3639	(96.6)	1817	(96.4)	1822	(96.7)	0.4111
	Yes	129	(3.4)	67	(3.6)	62	(3.3)	
Hemiplegia or paraplegia	No	3768	(100.0)	1884	(100.0)	1884	(100.0)	-
Renal disease	No	3759	(99.8)	1878	(99.7)	1881	(99.8)	0.3173
	Yes	9	(0.2)	6	(0.3)	3	(0.2)	
FECF - HCC incidence	No	3570	(94.7)	1711	(90.8)	1859	(98.7)	<0.001
	Yes	198	(5.3)	173	(9.2)	25	(1.3)	
AT - HCC incidence	No	3573	(94.8)	1711	(90.8)	1862	(98.8)	<0.001
	Yes	195	(5.2)	173	(9.2)	22	(1.2)	
FECF - All-cause mortality	No	3640	(96.6)	1766	(93.7)	1874	(99.5)	<0.001
	Yes	128	(3.4)	118	(6.3)	10	(0.5)	
AT - All-cause mortality	No	3641	(96.6)	1766	(93.7)	1875	(99.5)	<0.001
	Yes	127	(3.4)	118	(6.3)	9	(0.5)	
FECF - Liver-related mortality	No	3704	(98.3)	1827	(97.0)	1877	(99.6)	<0.001
	Yes	64	(1.7)	57	(3.0)	7	(0.4)	
AT - Liver-related mortality	No	3705	(98.3)	1827	(97.0)	1878	(99.7)	<0.001
	Yes	63	(1.7)	57	(3.0)	6	(0.3)	