**財團法人明日醫學基金會研究計畫申請書**

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| 計畫名稱 | （中文）慢性B型肝炎抗病毒治療使用不足與肝臟相關罹病與死亡風險的關聯性 |
| （英文）Association between underutilization of antiviral treatment for chronic hepatitis B and risks of liver-related mortality and morbidity |
| 計畫類別 | 🗹個別型 | 🞎整合型 |
| 計畫歸屬 | 🞎基礎醫學🞎生物醫學🗹臨床醫學🞎資訊系統🞎醫院管理🞎整合性醫學研究 |
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| 計畫執行期限 | 自 **110** 年 1 月 **1** 日起至 **110** 年 **12** 月 **31** 日止 |
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**研究計畫摘要**

**研究主題:** 釐清在台灣慢性B型肝炎抗病毒治療使用情形，並探討與肝臟相關疾病與死亡風險的關聯性

**ㄧ、試驗目的：**

1. 量化在台灣因為B肝抗病毒治療未被充分利用與肝臟相關罹病與死亡的關聯性

**二、研究背景：**

慢性B型肝炎是全球肝臟相關疾病和死亡的最主要病因，被核准的B肝抗病毒治療包括干擾素與核苷(酸)類似物，以往研究證實抗病毒治療可有效抑制病毒複製，並減少臨床事件諸如罹患肝細胞癌等風險；然而，各國對於抗病毒藥物適應症的規範並不相同，在台灣抗病毒治療使用情形也常受限於全民健康保險給付規定。臨床上，仍不時遇到B肝患者病情已進展至肝癌或因肝病死亡，卻一直未曾接受抗病毒治療，B肝抗病毒治療未被充分使用與肝臟相關疾病與死亡風險的關聯性，迄今仍未被釐清。

**三、研究方法：**

本研究為回溯性世代研究，將分析衛生福利部全民健康保險資料庫，從2000年至2018年台灣全人口資料，找出全國慢性B型肝炎患者（定義為特定疾病診斷碼與血清病毒學檢驗），根據抗病毒治療與否，分成下列組別：從未接受抗病毒治療者、僅接受過干擾素治療、僅接受過口服抗病毒藥物治療，以及接受過干擾素與口服藥物等四組，進行回溯分析。納入標準為成年(定義為年齡> 18歲)、由血清學檢驗確定B型肝炎感染、肝臟相關疾病與死亡，包括肝癌、肝功能不全引起的併發症，例如肝性腦病，靜脈曲張破裂出血，難治性腹水或慢性肝衰竭急性發作，以及與肝有關的死亡率（由死亡登記證明）；排除對象為無法確認慢性B型肝炎狀態(經由血清學檢驗、是否加入監測計劃、是否使用抗病毒治療，或特定診斷代碼來確認)，同時罹患丙型肝炎，或同時罹患人類免疫缺陷病毒感染的患者

**關鍵詞:**慢性B性肝炎；抗病毒治療；真實世界效益分析

**研究計畫目的及背景說明**

Consistent data from randomized controlled trials, real-world cohort studies, and laboratory experiments have demonstrated that antiviral therapy is effective to improve outcomes in patients with chronic hepatitis B (CHB).1, 2 Nonetheless, several lines of evidence suggest that antiviral treatment for CHB is currently underutilized in Taiwan where hepatocellular carcinoma (HCC) and hepatic failure remain the major causes of death.3 For instance, hepatitis B virus (HBV) infection has continued to be the leading etiology of HCC without changes in trend over time after antiviral treatment for CHB was reimbursed for by the national health insurance since 2003. The number of HBV-related HCCs remained invariably high with more than 3,500 new cases diagnosed every year in recent statistics update although the age-adjusted incidence might appear to decline.

Moreover, among the 2 million patients with CHB in Taiwan, less than one tenth (n=138,261 as of August 09, 2020 according to the bureau of national health insurance) are currently treated with antiviral therapy. In clinical practice, it is not uncommon to find CHB patients who progress to HCC, hepatic decompensation with clinical complications, or even liver-related death without having received antiviral therapy which could have prevented the progression.

The magnitude of underutilization, however, remains unclear in Taiwan. Furthermore, it needs to be clarified how the underutilization of CHB treatment is associated with excessive risks of liver-related mortality and morbidity at a population level. These findings will reveal gaps in the current practice where the opportunities to prevent adverse outcomes were missed and may thus inform healthcare policymaking to improve the linkage to care.

**研究假設**

Antiviral therapy for chronic hepatitis B is underutilized and is associated with excessive risks of liver-related morbidity and mortality in Taiwan

**主要目標**

To quantify the “missed opportunities” in preventing liver-related mortality and morbidity in Taiwan because of underutilization of antiviral treatment for CHB

**次要目標**

- To clarify the major causes for not having received antiviral therapy before CHB patients develop clinical complications

- To model how many events (HCC, hepatic decompensation, deaths) might have been prevented if a certain portion (a tuning parameter) of these patients had been given antiviral treatment

**研究方法及步驟：**

This is a nationwide population-based study that covers the entire Taiwanese population. We will analyze national healthcare databases that include health insurance research database, cancer registry, death certificate, and other vital statistics if applicable. Data contained in these databases are comprehensive and reliable not only because the national health insurance in Taiwan is compulsory and universal but also because certain policies such as the cancer control act and waiving patient copayment for catastrophic illness require data inspection and audition that help confirm accuracy of the recorded data. Besides, we have acquired accessibility to the registries of the surveillance program for patients with chronic viral hepatitis and the list of patients reimbursed for antiviral therapy over the years (since 2003). Moreover, through collaboration with the internal researchers inside the National Health Insurance Administration Ministry of Health and Welfare, we are now able to analyze data of laboratory results that were collected along with the healthcare service since 2016. Such data that include serum liver enzymes, viral serology (e.g., hepatitis B surface antigen, i.e., HBsAg, status), and measurements of viremia have been verified in our prior preliminary work. In short, familiarity with and accessibility to the aforementioned databases enable us to investigate our research questions with valid data at a nationwide scale.

To achieve our goals, first we will identify all patients who develop HCC, encounter the first episode of clinical complications as result of decompensated cirrhosis, first admission for acute on chronic liver failure, and liver-related mortality every year from 2004 to 2018 (the most updated data). Then these patients were classified as having CHB or not, which will be defined by HBsAg status (if available), enrollment in the surveillance program for chronic viral hepatitis, registry in the reimbursement list for antiviral therapy, or specific diagnostic code for CHB. For those patients who had not been tested for HBsAg status and was not diagnosed with HBV infection until occurrence of the aforementioned clinical events, we assume these patients had CHB because the vast majority of Taiwanese patients with CHB acquire HBV infection through vertical transmission or in infancy.

Among these CHB patients with late clinical events, we will identify those who had never received antiviral therapy until one month prior to the clinical event. Patients who receive antiviral therapy within one month prior to the event will not be excluded because the treatment could be given as a result of the event and a therapy shorter than one month is insufficient to prevent a late event. We will then calculate the number of these patients, characterize them in details, and examined the chronological changes over years. We’ll go on to analyze potential causes for not having been treated with antiviral therapy in these patients. The causes may be classified along the chain all the way from the diagnosis of CHB (e.g. never examined for HBsAg until the occurrence of a late event) to the national policy of antiviral therapy (e.g., patients with an established diagnosis of CHB and regularly followed up at specialists who could not initiate antiviral therapy because he or she did not fulfill the reimbursement criteria until occurrence of the late event).

Finally, we’ll estimate how many late events could have been prevented with administration of antiviral therapy by referencing studies which reported the effectiveness for reducing the risk of incident HCC, complications of decompensated cirrhosis, and liver-related mortality. As a more conservative approach, we assume at least 3 years of antiviral therapy will be needed to be effective.

***Statistical analysis***

There are about 2,000,000 Taiwanese residents with chronic hepatitis B. Each year, 3,500 people develop HCC and the number remains stable in the past 10 years. Nearly half of them (40~45%) are related to HBV infection. In short, we should be able to identify more than 15,000 CHB patients who developed HCC for our analysis. Taking into consideration the scenarios where CHB patients may progress to hepatic decompensation or pass away without developing HCC first, we are confident to identify at least 20,000 patients eligible for analysis.

Continuous data were summarized with median and interquartile range (IQR), whereas categorical data were presented with the exact number and proportion. The cumulative incidences of non-fatal events were estimated by semi-parametric analyses adjusted for competing mortality with the method developed by Gray. The incidence rate of each event was calculated by event occurrences per person-time for a specified time interval, and the trend over time was examined using Poisson regression for statistical significance.

Potential risk factors for underutilization of antiviral therapy were explored by logistic regression. Regardless of statistical significance in the univariable analysis, all variables were examined by a stepwise approach in the multivariable regression that retained statistically significant (prespecified as a P <0.05) variables in the final model. The analyses will be based on available information in the database without data imputation. Observations with missing data are thought to occur randomly and not included in the regression. Commercial software programs Stata (version 13.0, Stata Corp, College Station, TX, USA) and SAS (version 9.4, SAS Institute, Cary, NC, USA) will be used to manage and analyze the data. We computed all point estimates along with their 95% confidence intervals (CIs). All tests were two-sided with statistical significance defined as a P value <0.05.

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