財團法人明日醫學基金會研究計畫申請書

計畫名稱	（中文）監測中的慢性病毒性肝炎患者仍得到晚期肝癌的危險因子	
	（英文）Risk factors for late diagnosis of hepatocellular carcinoma in patients with chronic viral hepatitis under active surveillance	
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計畫主持人	姓名：許耀峻 Yao-Chun Hsu	機關：**義大醫院**
	職稱：**中心主任**	單位：**資料庫研究中心**
通訊地址	**高雄市燕巢區義大路 1 號**	
聯絡電話	**07-6155725, 0988687726**	
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共同主持人（一）	姓名：	機關：
	職稱：	單位：
共同主持人（二）	姓名：	機關：
	職稱：	單位：
共同主持人（三）	姓名：	機關：
	職稱：	單位：
共同主持人（四）	姓名：	機關：
	職稱：	單位：

研究計畫摘要

研究主題: 監測中的慢性病毒性肝炎患者仍得到晚期肝癌的危險因子

一、試驗目的：

探討慢性病毒性肝炎患者罹患肝癌無法被早期發現的原因,找出可預測監測失敗的危險因子

二、研究背景：

肝癌長期是國人主要的癌症死因，大部分的肝癌源自於長期慢性肝臟發炎，一旦慢性肝炎進展至肝硬化，患者每年有 5-10%的機會得到肝癌，在台灣慢性病毒性肝炎，包括 B 型和 C 型肝炎，是最主要的肝硬化及肝癌病因，超過 90%的肝癌與 B 或 C 型肝炎有關。有鑑於早期肝癌的治療效果與整體預後遠較末期肝癌好，因此為了早期發現肝癌，我國於 2010 年 1 月 1 日起實施<全民健康保險 B 型肝炎帶原者及 C 型肝炎感染者醫療給付改善方案>(以下簡稱改善方案)，以達成早期診斷早期治療的目標，方案規定參與者每半年需接受醫師診察評估，其中包含腹部超音波檢查。

然而，有效的肝癌篩檢與監測方式仍存在爭議，既存文獻對於影像工具，血液檢查，以及篩檢頻率等，仍未有一致結論。此外，仍有部分患者雖然已接受定期追蹤篩檢，可是發現肝癌時已非可治癒的早期癌，目前仍未有研究探討這些未被早期發現的肝癌患者，其監測失敗的原因與危險因子為何。

三、研究方法：

本研究擬採前瞻式世代研究，先找出已加入改善方案的慢性病毒性肝炎患者，追蹤後來的預後，是否得到肝癌。符合條件的病人須年滿 20 歲，B 型肝炎帶原者或 C 型肝炎感染患者(定義為 HBsAg 或 anti-HCV 陽性)， 入案前 6 個月內曾在收案醫院因B型肝炎或C型肝炎就醫至少 2次,B型肝炎患者需再檢驗 HBeAg, anti-HBe,收案時已接受肝功能指數及腹部超音波檢查，沒有發現肝癌。有下列條件者則予排除:曾罹患肝癌，曾有肝昏迷病史，未簽署同意書。

所有資料皆取自常規病歷紀錄。研究人員從電腦檔案記錄患者的病史、理學檢查結果、血液檢驗，影像檢查報告，是否得到肝癌其治療相關等等臨床資料，為單純觀察性研究，不涉及任何性質介入。俟資料收集彙整後，在分析前將先去除患者的身分識別，以編碼代號處理後續統計分析。

關鍵詞: 肝癌，慢性病毒性肝炎，篩檢計畫

研究計畫目的及背景說明

Hepatocellular carcinoma (HCC) is the fifth most common and the third most lethal malignancy worldwide, leading to approximately 600,000 deaths every year.[1] Hepatocellular carcinogenesis occurs predominantly in a chronically inflamed and fibrotic liver, with an annual incidence of 1.5 to 6% in patients with cirrhosis.[2] Globally and in Taiwan as well, chronic viral hepatitis with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection is the leading etiology of liver-related morbidity and mortality, accounting for the vast majority of HCC cases.[3]

There has been a tremendous progress in the antiviral treatment for chronic viral hepatitis in the past decade.[4] A growing body of data has demonstrated its efficacy in suppressing viral replication, ameliorating hepatitis, attenuating liver fibrosis, and delaying disease progression.[5,6] Even overt cirrhosis may regress after successful antiviral therapy.[7,8] Moreover, a growing body of evidence supports that treatment is associated with reduced occurrence and recurrence of HBV-related HCC.[10-14] However, some patients, especially those with existing cirrhosis, still go on to develop HCC despite taking antiviral regimen.

In view of the apparent risk for developing HCC, it has been suggested that patients with chronic viral hepatitis, regardless of taking antiviral drugs, should undergo active surveillance for HCC. Nevertheless, little has been elucidated regarding the time pattern and clinical predictors of HCC occurrence despite surveillance. In this study, we aim to investigate the chronological pattern and risk factors of a delayed diagnosis HCC in patients with hepatitis B or C under active surveillance.

研究方法及步驟：

（一）受試者選擇標準（Patient eligibility）

We will prospectively enroll all patients with chronic viral hepatitis who enter the national surveillance program for HCC in the E-Da Hospital and our collaborative hospitals (Lotung Poh-Ai Hospital and Tainan Municipal Hospital). All are adult (age > 20 years) patients who have been followed up for a least twice within 6 months in the managing hospital. Those who meet any of the following criteria are excluded: superimposed infection with human immunodeficiency virus, any malignant disease, organ transplantation, hepatic encephalopathy, and lack of informed consent. Cirrhosis can be either histopathologically or clinically diagnosed. Clinical diagnosis

is based principally on sonographic evaluation of liver surface, parenchyma, vascular structure, and splenomegaly.[17] We aim to enroll a total of 10,000 patients from 3 hospitals. Patients from different hospital will be used for independent validation.

(二)試驗設計與流程：

Surveillance for HCC

All enrolled patients receive HCC surveillance by means of ultrasonography and serum alpha-fetoprotein every 3~6 months. HCC was diagnosed according to the international guidelines.[2] The non-invasive diagnosis of HCC must fulfil characteristic features on dynamic images.[2] Patients were observed from the initiation of NUC therapy until the occurrence of HCC, death, loss to follow-up, or December 31, 2014

Assessment of clinical parameters and laboratory measurement

We will manually review and record pertinent clinical and laboratory data from the computerized database, including the behaviour of alcohol consumption with regard to the duration of drinking, types of beverage, and average amount of intake per day. Serology of HBV was assayed by immunoassays (ABBOTT GmbH& Co., Wiesbaden, Germany). The serum level of HBsAg was semi-quantified with the upper bound of 250 IU/mL, per the manufacturer's protocol. Viral DNA was measured by the branched DNA assay (VERSANT® 440 Molecular System., Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) before 1 May, 2010, and afterward by the real-time PCR method (Roche COBAS® TaqMan® 48; Roche Diagnostics, Basel, Switzerland). The detection range was 357 to 17,857,100 IU/mL for the former assay and 6 to 110,000,000 IU/mL for the latter method. The Model for End stage Liver Disease (MELD) score, the Aspartate aminotransferase (AST) to Platelet Ratio Index (APRI), and the Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B

(REACH-B) score were computed in line with the original formulas.[19-21]

（三）資料之蒐集處理評估及統計分析方法：

Continuous variables are expressed with median and interquartile range (IQR), and categorical variables with proportion. The Kaplan-Meier method is used to calculate the cumulative incidence of HCC, and the log rank test to examine the difference between groups. The unadjusted association between an explanatory parameter and HCC occurrence will be estimated by the univariate Cox proportional hazard analysis. Independent determinants of HCC are identified after adjustment for covariates from multivariate models developed with a stepwise manner. The results are reported as hazard ratio (HR) with 95% confidence interval (CI). All statistical analyses are two-sided and performed by use of the commercially available software (Stata, version 9.1; Stata Corp, College Station, TX, USA), a p value less than 0.05 considered as statistically significant.

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預期貢獻：

本研究預期找到肝癌無法被早期診斷的危險因子，若能達成此目標，吾人應可了解在現行監測改善方案下，哪些患者需特別密切追蹤以避免延誤肝癌診斷，以及進一步治療以降低肝癌對國人健康造成負擔。本研究對參與研究的個別患者沒有直接的預期效益。