財團法人明日醫學基金會研究計畫申請書

計畫名稱	（中文）決定慢性 B 型肝炎嚴重急性發作預後的病毒相關因子	
	（英文） Viral factors in determining outcomes of chronic hepatitis B patients with severe acute exacerbation	
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 **101** 年 1 月 **1** 日起至 **101** 年 **12** 月 **31** 日止	
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研究計畫摘要

一、試驗主題：

探討和慢性 B 型肝炎嚴重急性發作預後相關的病毒相關因子

二、研究背景：

嚴重急性發作是慢性 B 型肝炎獨特的併發症，導因於大量病毒複製所引發的細胞毒殺(cytotoxic)免疫反應，臨床上可快速進展到肝衰竭，雖然目前已有抗病毒藥物可用於治療，然而短期死亡率仍非常高，如何評估預後便十分重要。以往研究顯示肝臟衰竭的嚴重度與慢性肝病的程度是病人預後的主要指標，如果病人肝機能嚴重不全或者已有肝硬化，則死亡率可高達七成。

然而和病毒有關的因素，是否會影響這類病人的預後，仍未有定論。過往雖有相關研究，但是用來分析的病毒學方法並不敏感，比方說，過去的研究對於病毒 DNA 只有定性或定量的分析。因此，有必要以今日較敏感的病毒學方法再釐清。

三、研究目的：欲達成之主要目的與次要目的

主要目的:

探討和慢性 B 型肝炎嚴重急性發作預後相關的病毒相關因子

次要目的:

綜合本研究及以往文獻，發展慢性 B 型肝炎病人併發嚴重急性發作的治療流程

關鍵詞: 慢性 B 型肝炎，B 型肝炎病毒，肝機能代償不全，預後分析

研究計畫目的及背景說明

Chronic infection with hepatitis B virus (HBV) is a major liver disease worldwide, affecting 350 million people globally (1). Severe acute exacerbation is a unique complication of chronic hepatitis B (CHB) infection, resulting from massive viral reactivation and subsequent immune clearance that leads to extensive hepatic necroinflammation (2-4). Characterized clinically by abrupt elevation of serum aminotransferases along with jaundice, severe acute exacerbation of CHB is associated with high risk of morbidity and mortality (5, 6). Although timely antiviral treatment with oral nucleos(t)ide analogues may improve survival, a substantial proportion of treated patients still succumb to this devastating complication (7, 8).

Outcome determinants for severe acute exacerbation of CHB have not been fully elucidated. It is imperative to identify patients at risk of poor prognosis as early as possible, because acute on chronic liver failure (ACLF) may ensue rapidly and result in death in a short period of time unless liver transplantation can be performed in time (9, 10). Previous studies have demonstrated that mortality could be predicted by parameters that indicated severity of hepatic dysfunction (e.g. serum bilirubin, albumin, prothrombin time, and Child–Pugh score) and stage of underlying chronic liver disease (e.g. cirrhosis and platelet count) (6, 7, 11, 12). Not all fatal cases, nonetheless, initially manifested with profound hepatic failure or already had preexisting cirrhosis. It remained unknown how to further stratify risk of death in patients with relatively preserved liver function at initial presentation.

The role of viral factors in risk stratification has not been determined among CHB patients developing severe acute exacerbation. Earlier researches did not uncover association between pretreatment viral DNA and risk of death, but methods of measurement used in these studies were either only qualitative or very insensitive (6, 7). By using polymerase chain reaction (PCR) method, Jeng and colleagues were able to show that HBV DNA level predicted development of hepatic decompensation after episodes of acute exacerbation (13). Furthermore, Garg and colleagues recently reported in a randomized controlled trial that reduction of viral load after 2-week of antiviral therapy significantly correlated with chance of survival in patients with ACLF due to CHB (8). However, the relationship between pretreatment viremic burden and risk of mortality in these vulnerable patients remains elusive. We, therefore, set to investigate viral factors predictive of fatality in CHB patients with severe acute exacerbation.

研究方法及步驟：

(一)受試者選擇標準（Patient eligibility）

Study population:

This retrospective cohort study was conducted in a regional teaching hospital in Taiwan (E-Da Hospital, Kaohsiung City, Taiwan). We identified all treatment-naïve patients who received nucleos(t)ide analogues for severe acute exacerbation of CHB between November, 2004 and February, 2010. Those who met all of the inclusion criteria listed below were considered eligible: positive serum hepatitis B surface antigen (HBsAg) or unequivocal history of hepatitis B infection for more than 6 months, severe acute exacerbation defined as presence of both abrupt elevation of serum alanine aminotransferase (ALT) greater than 10 times the upper limit of normal and hyperbilirubinemia with serum total bilirubin level higher than 2 folds the upper limit of normal (14, 15), antiviral treatment with any nucleos(t)ide analogue, and detectable serum HBV DNA before treatment. Patients with any of the following exclusion criteria were excluded from analysis: super infection with other viral hepatitis (A, C, D, E), co-infection with human immunodeficiency virus, confirmed or suspected liver diseases from etiology other than HBV (alcohol, toxin, drug, shock, autoimmune, etc.), diagnosis of hepatocellular carcinoma, no data of pretreatment viral DNA, and previous exposure to antiviral therapy. Cirrhosis was clinically diagnosed principally on the basis of sonographic assessment (16). Development of encephalopathy and/or ascites within 4 weeks of presentation defined the condition of ACLF (9). The institutional review board of E-Da Hospital approved protocol of this study (protocol ID: EMRP-100-028).

(二)試驗設計與流程：

Management and follow-up

All enrolled patients received antiviral therapy with nucleos(t)ide analogues. Generally the daily dosages were 100mg for lamivudine, 0.5mg for entecavir, and 600mg for telbivudine but occasionally varied according to patients' conditions such as renal insufficiency. During the enrolment period, tenofovir was unavailable and adefovir was only reimbursed for the indication of rescue therapy in patients developing drug resistance. Some patients might initially receive a short course of combination therapy with 2 agents at the discretion of treating physicians. Every patient continued antiviral agent for a minimum of one year unless they died, acquired drug resistance, or were lost to follow-up. Add-on adefovir (10mg per day) was administered to those who later developed drug resistance. All patients were managed with standard supportive care in addition to antiviral medication. They might receive intravenous fluid, antibiotics, lactulose, albumin, proton pump inhibitor, and parenteral nutrition per individual indication. None of the enrolled participants underwent liver transplantation in that it was unavailable during the study period in this hospital.

In general, patients were hospitalized until severe flares and hepatic dysfunction

subsided. After discharge, they were followed up on a monthly basis for physical and biochemical examinations to monitor hepatic function. The interval between outpatient visits might be lengthened to 3-6 months in stabilized patients. This study cohort was followed up until September 1, 2011.

Laboratory measurement

Serological tests (HBsAg, anti-HBs, HBeAg, and anti-HBe) were determined by immunoassays (ABBOTT GmbH& Co., Wiesbaden, Germany). The upper bound in the semi-quantification of serum HBsAg was 250 IU/mL, as per the manufacturer's protocol. All pretreatment viral loads were measured by the quantitative method of branched DNA assay (VERSANT 440 Molecular System., Siemens Healthcare Diagnostics Inc., NY, USA), since not until May 1, 2010 was the more sensitive real-time PCR method available in this hospital. The detection range was 2000 to 10^8 copies/mL for the branched DNA assay. The expression of viral DNA was logarithmically transformed, and undetectable HBV DNA was taken as 1 copy/mL (0 log copies/mL) and enormous value beyond measurable range as 1,000,000,000 copies /mL (9 log copies/mL). Serum HBV was tested for signature mutations related to drug resistance for the administered drug in patients with confirmed virological breakthrough, which was defined as viral load rising higher than 10 folds above nadir.

（三）資料之蒐集處理評估及統計分析方法:

Data Analysis

Primary outcome of this study was survival rate during the follow-up period. We expressed continuous variables with median and interquartile range (IQR), and categorical variables with proportion. Survival curves were estimated by the Kaplan-Meier method and compared between groups by the log-rank test. Receiver operating characteristic curve was plotted to select the cut-off point of international normalized ratio (INR) for prothrombin time to predict mortality. The influence of pretreatment viral load on survival was further examined in the stratified analysis according to baseline INR. Cox proportional hazard model was developed to identify predictors associated with mortality. With all probable pretreatment covariates examined, we performed the multivariate analysis using forward and backward stepwise methods and assessed goodness-of-fit of the models. The results were reported as hazard ratio (HR) with 95% confidence interval (CI). The concordance rate between predictions and outcomes in all usable subjects was estimated by calculating the Harrell's C index (17). Statistical analyses were conducted using commercially available software (Stata, version 9.1; Stata Corp, College Station, TX, USA). All tests were two-sided with significance set at p value less than 0.05

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