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碩士論文

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Master Thesis

地區醫院B型肝炎病毒帶原者D型肝炎病毒共同感染的盛行率及其臨床影響

Prevalence and clinical impact of co-existing hepatitis D virus in patients with chronic hepatitis B virus infection in a district hospital

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本論文係李偉誠君（P07421313）在國立臺灣大學臨床醫學研究所完成之碩士學位論文，於民國 109 年 7 月 6 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

研究背景

D 型肝炎是一種缺陷病毒，無法獨立存在於人體，必須藉由 B 型肝炎病毒的幫助才能進行複製、傳播、感染其他肝細胞。之前全世界的盛行率約佔 B 型肝炎感染人口之 2-5%，雖然不多，但 D 型肝炎卻是目前所知肝炎中，預後最差者之一。

根據統計，合併 B 型及 D 型肝炎患者 10 年內有 70-80%會變成肝硬化，若進展到肝硬化，每年有 2.6-3.6%會進展到肝失代償，2.6-2.8%會進展到肝惡性腫瘤。

由於過去缺乏 D 型肝炎病毒感染的研究試劑，這個議題在台灣已經接近 20 年乏人研究，特別是在地區醫院層級，D 型肝炎病毒感染的狀況未曾被研究過。現在 D 型肝炎的臨床檢測試劑發展出來後，我們想藉由分析本院醫院 B 型肝炎帶原者中 D 型肝炎共同感染的盛行率及其臨床影響，提供其他醫療人員一個地區醫院 D 型肝炎的狀況，並提醒未來可能需要特別檢測追蹤 D 型肝炎病毒感染的病患族群。

研究方法

B 型肝炎患者會定期回診，追蹤時我們進行抽血檢查 AST、ALT、AFP 等肝功能指數，在抽血時加驗 Anti-HDV IgG，若患者 Anti-HDV IgG 陽性，則收案進行研究，預計檢驗 400 個 B 型肝炎個案，收 5 個 Anti-HDV 陽性個案並檢驗其血中的 HDV RNA。收集完後統計 B 型肝炎患者中，有 D 型肝炎病毒感染的比例有多少，並記錄比較 D 型肝炎病毒感染陽性與陰性兩個族群的年紀、性別、生化學檢查、腹部超音波發現以及是否有使用抗 B 型肝炎病毒藥物等。文獻上提到有 B 型肝炎患者若合併 D 型肝炎共同感染的患者有較高風險性進展到肝硬化，肝炎情形也更嚴重。我們將記錄本院的 B 肝與 D 型共同感染的患者是否也有類似情形。還有一些 B 型肝炎患者已經在服用抗病毒藥物，AST、ALT 卻仍然居高不下，是否也有可能是 D 型肝炎共同感染所造成的?同時，台大醫院也正在進行類似 D 型肝炎的研究，我們將比較永和耕莘醫院的資料與台大醫院的資料做對比，理論上臺大醫院是醫學中心而永和耕莘醫院是地區醫院，其病患組成應有所不同，我們將有機會分析兩院區 D 型肝炎共同感染病患臨床特徵之異同。

分析方式

1. 以 ANCOVA 分析並以邏輯回歸的方式校正年紀、性別的差異來比較 B 型肝炎 D

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型肝炎共同感染和單純 B 肝感染兩個族群間臨床表現的差別。

2. 以 ANCOVA 分析並以邏輯回歸的方式校正年紀、性別的差異來比較 B 型肝炎 D 型肝炎共同感染者在台大醫院和永和耕莘臨床表現的差別。

結果

在永和耕莘醫院我們共檢驗 346 人，驗出 D 型肝炎抗體陽性患者共 4 人，共同感染率為 1.15%。此 4 人血清中都沒有檢驗到 HDV RNA，肝硬化、肝癌、脾腫大、腹水發生率以及 e 抗原陽性的比率均為 0%。C 肝的共同感染率為 25%。沒有人在使用抗 B 型肝炎病毒藥。本院 B 型肝炎患者使用抗病毒藥族群中 ALT 仍然異常者都沒有 D 型肝炎病毒感染。D 型肝炎病毒抗體陽性和 D 型肝炎病毒抗體陰性兩個族群間相比臨床表現及生化資料均無顯著統計差別。

而台大醫院部份總共檢驗了 4361 人，檢驗出 D 型肝炎病毒抗體共 89 人，共同感染率 2.04%。其中 18 位 D 型肝炎病毒抗體陽性病患有填寫知情同意書而接受進一步檢驗，血清驗出 HDV RNA 陽性者 2 人。肝硬化比率為 22%、肝癌及腹水比率為 5.6%、脾腫大比率為 27.8%、e 抗原陽性比率為 11.1%。C 型肝肝的共同感染率為 0%。使用抗 B 型肝炎病毒藥物比率為 55.6%。而 D 型肝炎病毒抗體陽性的族群在永和耕莘醫院與台大醫院相比，臨床表現及生化資料亦無顯著統計差別。

討論

1. D 型肝炎病毒感染的盛行率

D 型肝炎病毒感染在全球各地區的盛行率差異很大，台灣地區根據台北榮總吳肇卿教授所做的研究，D 型肝炎病毒感染盛行率在 1985-1997 年間快速的減少，從 23%下降到 4%。吳教授把這樣的結果歸因於政府這些年來不斷推動 B 肝防治計畫與性病防治政令宣導、禁娼、禁毒，以致 D 型肝炎病毒感染的傳染路徑被阻斷有關。

但在 2000 年後 D 型肝炎相關文獻較少，只有 2015 年台北榮總吳肇卿教授與 2018 年林口長庚葉昭廷教授有發表盛行率。兩篇研究的盛行率均為 4.4%。相較於兩篇文章，本研究是目前最新統計的資料，收案時間為 2019 年，D 型肝炎病毒感染盛行率在永和耕莘醫院為 1.15%，在台大醫院為 2.04%。此盛行率的下降再次反應出我國公衛防治的成功，有效阻絕 D 型肝炎病毒的傳播。而永和耕莘醫院的盛行率僅台大一半，可能因為永和耕莘醫院僅是地區醫院，嚴重個案可能已經轉診，

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導致病患的嚴重性與複雜性都較醫學中心為低,D 型肝炎病毒共同感染率也較低。

2. D 型肝炎病毒抗體陽性與陰性患者在臨床表現上比較

之前多數研究都指出，D 型肝炎是已知病毒性肝炎中最嚴重的一種，但並非每個研究都如此,過去 20 年來就有兩篇台灣的研究認為 D 型肝炎病患相比於單純 B 肝病患之臨床特徵並無差異 (2004 年廖運範教授、2000 年吳肇卿教授)。本研究中，D 型肝炎病毒抗體陽性組相比於陰性組，在臨床特徵、血清及生化學數據上兩組均無顯著差異。部分的原因跟之前兩篇台灣研究相對照，會令人聯想是否台灣的 D 型肝炎病毒基因型與國外不同,所以臨床症狀比較輕微,可惜在本研究中，無法檢驗 D 型肝炎病毒基因型而加以證實。還有一個可能就是跟血清病毒陽性率有關，2019 Dr. Adriana 的研究指出病情的進展與病毒血清陽性率呈正相關。本研究因 4 名 D 型肝炎患者血中均無驗出 D 型肝炎病毒，可能對病患肝臟發炎的影響亦有限，所以兩組之間無統計差異。

3. 血清 D 型肝炎病毒陽性率

在之前的研究中，D 型肝炎患者 80%以上會變成慢性帶原者，血清 D 型肝炎病毒陽性率理論上應該在 70-80%之間，但在不同研究中差異很大。在本研究中血清 D 型肝炎病毒陽性率僅 9.1% (2/22)，這部分我們做出一個大膽的假設：D 型肝炎病毒在經過早年性病防治、宣導、篩檢的政策執行下，已經很難有新的感染者了。當年 (1980 年)之前得到的 D 型肝炎可以分成兩群：80%帶原者 (血清有 D 型肝炎病毒)快速進展到肝硬化、肝癌而死亡；其他 20%復原者 (血清無 D 型肝炎病毒)因沒有症狀而可以存活很久。這可以解釋為什麼之前研究中 D 型肝炎盛行率從 1985-1997 年 23%下降到 4%後(80%帶原者快速死亡)，在接下來 20 年間盛行率都維持不變，因為剩下者大多是無 D 型肝炎病毒者，臨床症狀本就不明顯，存活時間也不受影響。

4. D 型肝炎病毒抗體陽性組在永和耕莘醫院與台大醫院的比較

兩者在臨床特徵、血清及生化學數據亦無統計學上的差異。此原因可能是樣本數過低 (永耕 4 人；台大 18 人)，以及這些病患的血清病毒陽性率過低導致臨床症狀本就不明顯，導致統計上難有差異。

5. D 型肝炎患者接觸史

過去的研究指出 D 型肝炎病毒傳播可藉由血液、性行為接觸,故在毒癮患者、

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嫖妓行為、HIV 族群特別高。但本研究中 D 型肝炎患者幾乎沒有接觸史 (22 人只有 1 人之前為毒癮患者)，跟之前研究相比有落差。可能因為接觸史的了解是由門診時醫師或研究助理口頭詢問，這部分牽涉到隱私，回答的真實度可能有疑問。

結論

在近年政府全面 B 型肝炎疫苗施打計畫及政令宣導下，D 型肝炎人數已逐漸下降，但並未滅絕。在永和耕莘醫院這個地區醫院的研究上看來，D 型肝炎病毒感染盛行率比醫學中心低，其臨床影響也不大，但畢竟因樣本數比較少，難以代表全國其他社區的狀況，未來應擴大 D 型肝炎的篩檢範圍及對象，以進行更深入的研究。

關鍵字: D 型肝炎、盛行率、共同感染、B 型肝炎、臨床影響

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英文摘要

Purpose.

Prevalence and clinical impact of hepatitis D virus infection in Taiwan's communities remained unclear and was thus investigated.

Background.

Hepatitis D virus (HDV) is a defective RNA virus, which needs help of hepatitis B surface antigen (HBsAg) to enter hepatocyte for replication, assembly and transmission. Besides, HDV is believed to be one of the most severe form viral hepatitis, which lead to cirrhosis and hepatoma in majority within 10 years after infection. Hepatitis B virus (HBV) infection is endemic in Taiwan; however, only few studies evaluated prevalence and clinical impact of HDV recently, particularly in community hospitals. Therefore, we conducted this study in a district community hospital.

Materials and Methods.

HDV infection in all patients with HBV infection was examined by usinging anti-HDV antibody in Yonghe Cardinal Tien Hospital (YCTH), a district hospital in Taiwan. The demographic, clinical and serologic characteristics and contact history were recored. After informed consent, the serum HDV RNA was also determined by a commercial assay.

The clinical characteristics of the patients with anti-HDV positivity versus negativity were compared. At the same time, similar screening and assessment were done in a medical center, National Taiwan University Hospital (NTUH). These clinical and virologic features were also compared with those patients collected from this medical center. The comparisons of continuous variables and adjustment for confounding factors were conducted by using the analysis of covariance method, while the comparisons of category variables were conducted by using the logistic regression method.

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Results.

Totally 346 patients with chronicHBV infection were collected assessed for serum anti-HDV during 2019 to 2020. Of them, 4 (1.15%) were positive for anti-HDV. The clinical, virological and biochemistry characteristics were similar between anti-HDV-positive and -negative groups. None of the 4 patients was positive for serum HDV RNA. One patient had history of using illegal drugs but the others denied using illegal drug or exposure of prostitution. Another 18 anti-HDV positive patients were identified from NTUH. 2 of the 18 patients were positive for serum HDV RNA. None of the 18 patients had history of using illegal drug or exposure of prostitution. The clinical, virological and biochemistry characteristics in anti-HDV positive groups between YCTH and NTUH were also similar.

Discussion

1. Prevelance of anti-HDV: Prevalence of anti-HDV decreased from 23% to 4% during 1985-1997 and remained around 4-5% during 2000-2018 according to previous studies. Our study showed the latest data, which was collected in 2019. The prevalence of anti-HDV was 2.04% in NTUH and 1.15% in YCTH. The decline of anti-HDV prevalence rate reflected the effort of our government to promote health public policy which blocked transmission of HBV as well as HDV infection.
2. The clinical characteristics of anti-HDV positive versus negative patients: although previous studies suggested HDV infection to be one of the most severe form viral hepatitis, two studies from Taiwan had different findings. In our study, no significant differenc between anti-HDV positive and negative group was found. One reason might be due to distribution of HDV genotype. Some researchers believed HDV genotype 4 had mild clinical presentations and progression; however, we did’t perform HDV genotyping in this study. The other reason was probably due to low

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positive rate of serum HDV RNA. In our study, none of the 4 patients in YCTH and only 2 of 18 patients in NTUH had detectable serum HDV RNA. Inactive HDV infection may be associated with mild clinical symptoms; so no significant differenc between HDV positive and negative group was noted.

3. Low serum positive rate of HDV RNA: the positive rate of serum HDV RNA varied widely in the world. In our study only 9.1% (2/22) of the anti-HDV positive patients had detectable serum HDV RNA. Detection sensitivity of the commercial kit for serum HDV RNA should be validated further.
4. The clinical characteristics of HDV positive patients in YCTH versus NTUH: in our study, clinical characteristics of HDV positive patients between YCTH and NTUH had no difference. This findings suggested that the clinical profile of anti-HDV positive patients in district hospitals was similar to those in medical centers.
5. HDV contact history: although previous studies revealed the high correlation between HDV and illegal drug usage and exposure of prostitution, only one patient in our stuy had history illegal drug use and the others all denied contact of illegal drug or prostitution. The possibility of information and recall bias should be considered.

6. Conclusions.

The prevalence of anti-HDV in local hospital was low, so as the serum HDV RNA positive rate. Co-existing HDV infection did not influence the clinical manifestation of patients with chronic HBV infection in Taiwan.

Keywords. Hepatitis D virus, prevalence, coinfection, hepatitis B virus, clinical impact

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Revisiting the Prevalence and Clinical Impact of Hepatitis Delta Virus Infection in Taiwan

一、 Introduction

HBV infection is endemic in Taiwan, with the prevalence rate up to 15% in the adult population and causing serious public health problems. For examples, hepatocellular carcinoma (HCC), the second among the top ten cancer causes of death, and liver cirrhosis with decompensation, the tenth among the top ten leading causes of death, are mainly due to chronic HBV infection. To control this infectious disease, national vaccination program against HBV transmission was launched since 1984 in Taiwan; and the HBV prevalence rate in the young generations has declined gradually from 15% to ~1% nowadays [1]. Besides, several potent and anti-viral agents with high genetic barrier were administered widely for the treatment of patients with chronic active hepatitis B, such as entecavir, tenofovir disoprxil furamate, and tenofovir alafenamide [2] [3]. However, there were still unmet needs for the management of HBV infection in Taiwan. For examples, some patients had persistent abnormal liver function despite taking potent anti-HBV agents, which reminded us the possibility of hepatitis D virus (HDV) co-infection or other etiologies such as non-alcoholic fatty liver disease.

HDV is discovered by Rizzetto and colleagues in the mid-1970s, with a spherical shape and about 36 nm in diameter [4]. HDV genome is a single-stranded, circular RNA containing approximately 1700 nucleotides, and about 200 molecules of hepatitis D antigen (HDAg) [5]. HDAg has two isoforms, which are small HDAg (S-HDAg) composing 195 amino acids and large HDAg (L-HDAg) composing 214 amino acids. HDV is more related to plant viroids than animal virus due to the high GC content of

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the nucleotides sequences [6], and its defective structural nature needing help of hepatitis B surface antigen (HBsAg) to enter hepatocyte for replication, assembly and transmission of new virions [7]. Clinically, HDV infection occurs only in the presence of hepatitis B virus (HBV), either in patients already infected with HBV (super-infection) or simultaneously infected by both HDV and HBV (co-infection) [7]. Super-infection and co-infection had similar symptoms initially but with quite different clinical outcomes. Co-infected patients usually recover after acute HBV/HDV infection; however, HDV super-infected patients often become chronic carriers with rapid disease progression [5]. Several studies suggested chronic HDV infection to be one of the most severe types of viral hepatitis, with an increased 3 times risk of cirrhosis, liver decompensation and hepatocellular carcinoma within 10 years from the onset of acute hepatitis D [8-11]. On the other hand, treatment of HDV was a challenge. Despite the progress in the treatment of chronic HBV and HCV, interferon-α still remains the only drug used for HDV treatment and the response rate was poor. One-year high dose interferon treatment only induced 10% to 20% sustained HDV clearance and 10% HBsAg clearance rate [12]. Anti-HBV drugs such as lamivudine and tenofovir did not help HDV clearance with or without interferon [12]. Three new classes of drugs are now under development: Myrcludex B, Lonafarnib and REP 2139[13]. Myrcludex is a hepatitis D virus entry inhibitor, which inhibit HBV and HDV entry into cell by competitively blocking NTCP, the key transporter responding for HBV and HDV entry. Lonafarnib is a virus assembly Inhibitor, which interfere HDV assembly by inhibiting farnesylation, a key step of anchoring HDV RNP into HBsAg. REP 2139 is nucleic acid polymers, which are oligonucleotides with broad-spectrum inhibitory activity against several viruses including HBV. Clinical trials using these three classes of new drugs are still ongoing [14-18].

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The prevalence of HDV super-infection in HBsAg carrier was reported up to 8% [19] around 1980. The HBV prevalence rate in Taiwan had declined gradually after launching of national vaccination program. Theoretically, HDV prevalence rate may decline in parallel. Unfortunately in the last decade, very few studies had addressed this issue. One study conducted in medical center in 2015 revealed low anti-HDV prevalence (4.4%) in the HBV-infected population, but significantly higher prevalence rates in patients with human immunodeficiency virus (HIV) infection (43.9%), intravenous drug users (IDU) (11.9%) and highest in those with both risk factors (74.9%) [20]. Notably, the result was obtained from tertiary referral center; prevalence data from local community and general population was not clarified yet. Furthermore, patients from medical center may be more serious than those followed in local hospital, and the risk behaviors associated with HDV infection may also be different. Patients with critical illness or serious infectious diseases would be transferred to medical center. For example, HIV treatment is not approved in local hospital so those patients would be transferred to medical center while diagnosed, so as patients other critical disease such as malignancy or decompensated liver cirrhosis. Accordingly, patients visiting local hospital are more likely represent general population. However, no study was done yet to address these issues in local or regional hospital. We thus conducted this study in Yonghe Cardinal Tien Hospital (YCTH), a local community hospital in New Taipei City. We compared the prevalence, severity and risk factors associated with HDV infection in local hospital versus medical center.

二、 MATERIALS AND METHODS

2.1 Study population

A flow diaphragm summarizing this study is illustrated in Figure 1. We collected

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all patients with chronic HBV infection from a local hospital (YCTH), and tested serum anti-HDV by a commercial assay. After informed consent, patients positive for serum anti-HDV were further tested for serum HDV RNA; and we collected history and information about risk behaviors from these patients.

For the other HBsAg carriers negative for serum anti-HDV, we retrospectively collected their clinical, serologic and virologic data from the chart. To clarify whether the risk factors, clinical or virologic features of patients positive for anti-HDV in this local hospital were different from those patients collected from medical centers, 18 anti-HDV-positive patients from National Taiwan University Hospital (NTUH), a medical center in Northern Taiwan, were also collected as controls.

2.2 Clinical and virological factors associated with anti-HDV

Their demographic and laboratory date including age, gender, hemogram, liver function test, HBsAg titer, ant-HBV treatment history and ultrasonographic examination of the abdomen were collected from charts and interviews. Diagnosis of liver cirrhosis was made based on: any sign of portal hypertension, ultrasonographic finding of small and coarse echogenicity of liver with round edges, or fibrosis-4 index value > 6.5. Infection with HDV was defined as positive anti-HDV Ab in chronic HBsAg carriers.

2.3 Serological viral markers

The assay of anti-HDV immunosorbent enzyme developed by General Biologicals Corporation (Name of kit???, Hsinchu, Taiwan) was used in this study. The quantification of serum HBV DNA was determined by using the Cobas TaqMan with a lower limit of detection of 6 IU/mL (Roche Diagnostics, Mannheim, Germany). Serum HDV RNA was detected using real-time PCR (RoboGene® HDV RNA Quantification Kit 2.0, Leipzig, Germany). The detection limit of real-time PCR assay was 106

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copies/mL. The sensitivity and specificity of this assay was 100.0% (95% confidence interval [CI], 88.3%-100.0%) and 99.0% (95% CI, 97.9%-99.6%), respectively, according to the manufacturer's instructions[21]. This device was the standard for Hepatitis D virus RNA for Nucleic Acid Amplification Techniques (NAT)-Based Assays and approved by the World Health Organization (PEI code 7657/12).

2.4 Ethical considerations

The study protocol was approved by the institutional review board of YCTH (number CTH-107-2-5-062) and NTUH (number 201904075RINA). Serum HDV RNA was determined, and risk behavior information and serum samples were collected after informed consent.

2.5 Statistical analysis

The clinical characteristics of the subjects with anti-HDV positivity and negativity were compared. The comparisons with category responses were adjusted with age and gender under the logistic regression method. Also, the clinical characteristics of the subjects with anti-HDV positivity from the two hospitals were compared. The comparisons with continuous responses and category responses were, respectively, adjusted with age and gender under the analysis of covariance (ANCOVA) model and logistic regression model.

三、 Results

3.1 Anti-HDV positive group in YCTH

From the database of the Yonghe Cardinal Tien Hospital (YCTH) between Jan. 1st 2019 and Dec. 31st 2019, a total of 346 individuals were identified to be serologically positive for HBsAg. Serum anti-HDV antibody was checked in all of these cases.

Among 346 patients, 4 (1.15%) were found to be positive for anti-HDV antibody;

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their data are shown in Table 1 and Table 2. Of the 4 cases, male gender was predominant (3/4, 75%), and mean age was 53.75 years. Serum HBeAg were all negative for the 4 anti-HDV-positive patients (0/4). Serum HBV DNA could be detected in one patient (562 IU/ml) and was undetectable in the other three patients. Mean serum ALT was 33.8 ± 14.6 U/L. None of the 4 patients had evidence of liver cirrhosis or history of receiving anti-HBV treatment. Serum HDV RNA was undetectable in all 4 patients. One male was illegal drug user and all the other patients denied unusual sexual contact or prostitution activities. One male patient had HCV co-infection and all the other were anti-HIV-negative.

3.2 Anti-HDV positive group in NTUH

In Taiwan National University Hospital (NTUH), a total of 4361 HBsAg carriers were tested for anti-HDV antibody between Jan. 1st 2018 and Nov. 30st 2018. Among these 4361 carriers, 89 (2.04%) were positive for anti-HDV. Of them, 18 of 89 patients were enrolled after obtaining informed consent. Their clinical data are shown in Table 3 and Table 4. Of the 18 cases, male gender was predominant (78%), and mean age was 60.56 years. Two of them were positive for serum HBeAg (11.1%) and 5 of them had detectable serum HBV DNA (28%). Mean serum ALT level was 44.2 ± 30.8 U/L. Four of them had evidence of liver cirrhosis (22%) and 10 of them received anti-HBV treatment (56%). Serum HDV RNA could only be detected in 2 (11%) of the 18 patients; the serum HDV RNA level was 82000 IU/ml and 150 IU/ml, respectively. None of them were illegal drug user and all denied unusual sexual contact or prostitution activities, either. Besides, none of them had HCV co-infection.

3.3 Anti-HDV positive group versus anti-HDV negative group; clinical and virological characteristics

The clinical and virological characteristics of the 4 anti-HDV positive and 342

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anti-HDV negative groups in our local hospital are shown in Table 5 and Table 6. All clinical and virological characteristics of the anti-HDV-positive and anti-HDV-negative groups were not significantly different, including proportion of cirrhosis, splenomegaly, ascites, stage of liver fibrosis, history of HCC, positivity of HBeAg, history of anti-HBV treatment and the presence of HCV co-infection.

3.4 Anti-HDV positive group versus anti-HDV negative group; biochemistry characteristics

The biochemical characteristics of the 4 anti-HDV positive and 342 anti-HDV negative groups are shown in Table 7. The biolochemical characteristics of anti-HDV positive and anti-HDV negative groups were not statistically different, either, including white blood cell count (WBC), hemoglobin (Hb), platelet count, international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, creatinine and alpha-fetoprotein (AFP).

3.5 Clinical and virological characteristics of anti-HDV positive patients: Comparison between YCTH patients and NTUH patients

The clinical and virological characteristics of the 4 anti-HDV positive patients in YCTH and 18 anti-HDV positive patients in NTUH are shown in Table 8 and Table 9. All clinical and virological characteristics of the NTUH and YCTH groups were not significantly different, including proportion of cirrhosis, splenomegaly, ascites, stage of liver fibrosis, HCC, positive HBeAg, HBV treatment and HCV co-infection.

3.6 Biochemical characteristics of anti-HDV positive patients: Comparison between YCTH patients and NTUH patients

The biochemical characteristics of the 4 anti-HDV positive in YCTH group and 18 anti-HDV positive in NTUH group are shown in Table 10. The biochemical characteristics of the two groups were similar regarding WBC, Hb, platelet, INR, AST,

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ALT, total bilirubin, albumin, creatinine and AFP.

四、 Discussion

To our knowledge, HDV-related issues in local hospital were never studied and the difference between local hospital and medical center was not known, either. Therefore, we first examined the prevalence and clinical impact of HDV infection in YCTH, and then compared the clinical, virological and biochemical characteristics of HDV-infected patients in YCTH versus the anti-HDV-positived patients in NTUH.

In our study, the prevalence of HDV in YCTH was 1.15% (4/346), and serum HDV RNA positive rate was 0% (0/4). There was no clinical difference between anti-HDV positive patients and negative patients statistically after adjusting with age and gender. On the other hand, the prevalence of HDV in NTUH was 2.04% (89/4361). We studied 18 of 89 patients and found serum HDV RNA positive rate was 11.1% (2/18). There was also no clinical difference in HDV positive patients between YCTH and NTUH statistically after adjusting with age and gender. For the contact history; only 1 patient had used illegal drug and all others denied using illegal drugs or prostitution.

The global prevalence of HDV varied widely in previous studies. Around 13 to 15% of the hepatitis B carriers are found to have HDV infection in a recent meta-analysis [11,22]. Anti-HDV is highly endemic in mediterranean countries, the middle east, Central Africa, and northern parts of south America [23]. Taiwan is a highly endemic country of HBV infection during past decades, with an extremely high prevalence of chronic hepatitis B infection in the general population (15 to 20%) around 1975. The government noticed this health problem then initiated a mass vaccination program against hepatitis B for newborn infants since 1986. Twenty years after the program being conducted, the hepatitis B carrier rate of newborn decreased from 15% to < 1%

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[24]. The prevalence of HDV infection in HBV-infected population in Taiwan also decreased in these decades (23.7% to 4.2% from June 1983 to May 1995), probably due to vaccination programs and a series of public health policy including screening HBsAg for blood donor, promotion of disposable needles, active education of HBV carriers, drug abuse prevention, HIV prevention and inhibition of prostitution [25]. However, the declining trend did not persisted in the next 20 years. The prevalence was still up to 4.4% in Taipei Veterans General Hospital (VGH) since 2001 to 2012 [20] and 4.4% in Chang Gung Memorial Hospital, Linkou (CGMH) since 2006 to 2018 among all HBV carriers [21].

In our study, we provided the latest prevalence of anti-HDV positivity, which was 2.04% in NTUH and 1.15% in YCTH of HBV-infected population since 2019 to 2020. NTUH is a tertiary medical center, same as VGH and CGMH with similar patient composition and characteristics. The reason of a lower prevalence rate of anti-HDV positivity in NTUH as compared to VGH and CGMH may be due to the legacy effect of HBV vaccination and public health policy which further blocked the transmission route of HDV, it also reflected the fact that our public health work did really good. In YCTH, the prevalence of HDV was even lower than that in NTUH. The first reason was that YCTH is a local hospital, with patients being less severe clinically. Previous studies revealed higher rates of cirrhosis and disease progress in patients with HDV so those severe cases may mostly be transferred to medical center. The second reason may be the small numbers of HBV population in YCTH (only 346 patients versus 4361 in NTUH), such few cases may cause statistically bias. On the other hand, HDV is known with higher prevalence in population with IDU and prostitution. Only one of our 22 patients admitted to be an ID user, all other patients denied IDU or prostitution. Nevertheless, the history is taken by interview with the medical assistance so the reality may be

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questionable.

HDV is believed to be the most severe form of viral hepatitis. According to previous study, approximately 70 to 80% HDV carriers may develop cirrhosis within 10 years after acute infection [26]. After cirrhosis, The annual incidence of liver decompensation in HDV cirrhosis ranges from 2.6% to 3.6% and from 2.6% to 2.8% for HCC [9]. A meta-analysis published in 2019 by Dr. Miao showed similar result, which HDV infection progresses to cirrhosis within 5 years and to hepatocellular carcinoma within 10 years in average [11]. However, in our study, there is no significant difference between HDV-positive and negative groups, no matter clinically, virologically or biochemistry. That could result from small number of positive group (only 4 cases). It seemed to be weird but actually it is not the only one study to show minimal impact of HDV in clinical aspect. Two previous studies published in Taiwan by Dr. Liaw in 2004 [27] and by Dr. Huo in 2000 [28] also had similar results that HDV group did not have worse clinical progression or higher rate of liver cirrhosis, which implicated us the possible impact of HDV genotype. There were eight HDV genotypes discovered in previous studies. Although not well understood, different genotypes of HDV did have different clinical characteristics. For examination, HDV-1 genotype had poor response rate to interferon treatment and worse adverse outcome than HDV-2 genotype [29] and HDV-4 genotype had milder disease [30]. Maybe HDV-4 genotype was dominant in Taiwan population; however, HDV genotyping was not available in our study due to technological limit. Another possible reason may be due to the low HDV RNA serum positive rate. One recent study published in 2019 by Dr. Adriana found subjects with detectable HDV RNA had much higher risk to developing cirrhosis (31% vs 0%, P = .002) and/or liver decompensation (28% vs 3%, P = .0019) and mortality [31]. Back to our study, most of our subjects (2/22, 9.01%) can't detect HDV RNA in serum,

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which may be the reason why our anti-HDV positive group did not have worse clinical outcome than anti-HDV negative group.

HDV can be transmitted simultaneously with HBV infection (co-infection) but mostly in an individual already chronically infected with HBV (super-infection) [32], the latter result in chronic infection in around 80% of cases. However, the detection rate of serum HDV RNA in anti-HDV positive population varied in previous studies. For example, the serum HDV RNA positive rate may be low to 9% in Nigeria, 20% in London, 43% in Taiwan [20], 73% in Spain [31], 33% in Italy and higher to 97.9% in Mongolia [33]. However, in our study serum HDV RNA was detected only in 2 out of 22 patients (9.1% serum HDV RNA positive rate), significant lower than previous studies. Considering the fact of low but persistent prevalence around 4% since 1995 to 2018, low HDV serum positive rate and less clinical impact, we had one hypothesis. After the great effort of public health program on inhibiting prostitution and narcotics, the transmission of HDV should be mostly blocked. In 1980s, 80% infected HDV patients became chronic carriers with positive serum HDV RNA and soon progressed to cirrhosis or hepatoma in 10 years then expired, but the other 20% HDV patients spontaneously recovered with negative serum HDV RNA and survived for more than 20 years. That is the reason why prevalence stasis at 4% in recent 20 years and the anti-HDV positive group had such low serum HDV RNA positive rate. Then the anti-HDV positive group had such less clinical impact.

Last but not the least, anti-HDV positive groups in YCTH and NTUH had no significant difference in clinical, virological or biochemical characteristics. YCTH is a local, community hospital, while NTUH is a tertiary medical center. Objectively, patients in NTUH might be more critical and have more co-morbidity than patients in YCTH, however, that is not seen in our study. First reason might be the small number of

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cases (4 versus 18), and second reason might be the relative weak clinical impact of HDV in our study.

五、 Summary

Anti-HDV positivity prevalence rate was 1.15% in YCTH, 2.05% in NTUH, lower than those in previous studies in Taiwan, probably due to the legacy effect of our public health program on inhibition of prostitution and narcotics. We found 22 patients with positive anti-HDV Ab but only 2 of them had detectable HDV RNA in serum. Maybe due to low percentage of viremia, the group with positive anti-HDV did not have poorer outcome then group with negative anti-HDV. Besides, due to low clinical impact, anti-HDV positive group in medical center did not have poorer outcome then in local, community hospital. However, the studied population is small. Further and bigger studies are needed in the future.

六、 Clinical implication

HDV infection is a relative rare disease without fully studied in Taiwan. Our studied revealed the prevalence and clinical characteristic in a local hospital. Surprisingly, the prevalence was low and the clinical characteristics were not worse and the infection route was unclear. After long time effort of HBV vaccination, public health policy against narcotics and sexual transmitted disease in Taiwan, HDV are decreasing but not totally eliminated. Luckily, it may not worsen clinical course if serum RNA was undetectable, regularly follow should be needed in the future but aggressive treatment such as interferon might not be needed. HDV may not always be with IDU, HIV or prostitution so the screening work should be done to all HBV patients rather than limited in specific population.

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Second, the prevalence of NTUH was higher than local hospital but lower than previous studies in other medical center, besides, the clinical characteristics were similar in local hospital. It might hint us although HDV was decreasing and under control. With well education and discussion, those patients can avoid transmit to others. Someday, HDV may be total eliminated in Taiwan.

七、 Limitation

1. Case number is very small; only 22 anti-HDV positive subjects were enrolled from two hospitals. Furthermore, there were too many missing data in the anti-HDV negative group; therefore information bias may occur in this retrospective study

2. The contact history of IDU and prostitute were taken by interview with medical assistance. The reality is questionable and could not be validated in this study.

3. Relatively few patients with positive anti-HDV in NTUH could be assessed due to IRB restriction. This selected cohort may not represent the general anti-HDV positive population in this medical center.

4. Totally only 44 HBV patients received active anti-HBV treatment, and none of 4 with HDV co-infection received anti-HBV treatment, which make it difficult to evaluate whether persistent elevated ALT during anti-HBV treatment were related to concurrent HDV infection or not.

5. The study was retrospective and cross-sectional. We could not clarify the exact duration of HDV infection. Whether the clinical progression of HBV infection was partly related to concurrent HDV infection need large long-term follow-up.

6. The lower limit of HDV RNA assay is 106 copies/mL. HDV viral load lower than 106 copies/mL would be identified as “undetectable”, which may be a bias for those with low DNA copy number.

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7. HDV genotyping was unavailable in our study. Different HDV genotypes had different clinical characteristics and outcome. This part need modified in the future.

八、 Conclusions and perspectives

Twenty years after the launch of HBV vaccine program, the population of HDV decreased with HBV but not eliminated. Our study revealed the current epidemiological, virological, biochemical and clinical status of HDV. The result, transmission route and clinical impact seemed different with our previous knowledge. Current positive anti-HDV patients need to be followed in the future, keeping this study prospectively. On the other hand, we would try to assess all other patients with positive and negative anti-HDV in NTUH by granting IRB permission, which may give us information more completely.

As HBV is still a major health issue in Taiwan, doctors are also working on eliminating HBV. HDV might play a role in the future, related issues still worth further studies to estimate and evaluate.

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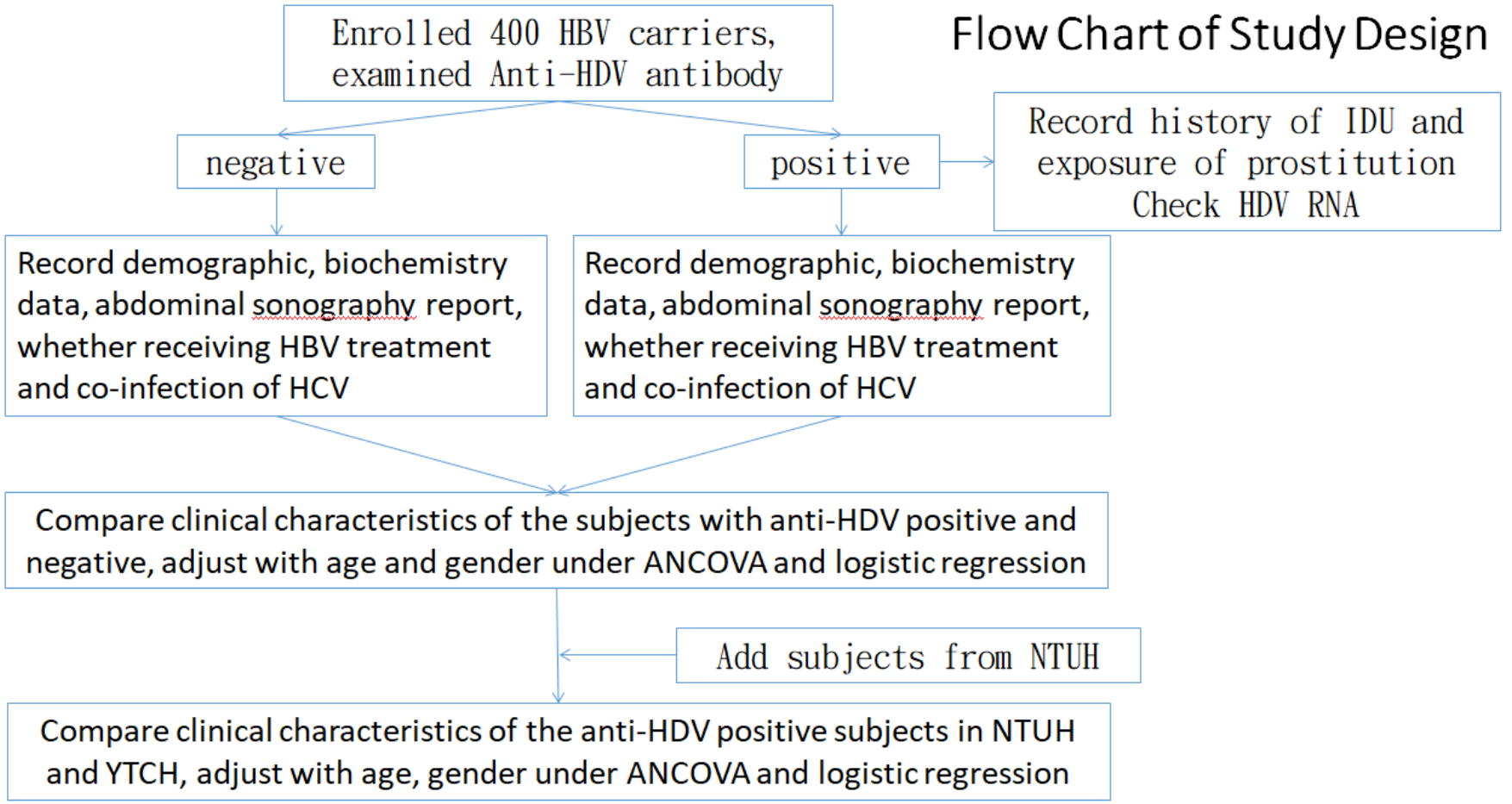
十、 **Figure 1. Flow Chart of Study design**



- NTUH: National Taiwan University Hospital
- YTCH: YongHe Tien Cardinal Hospital

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- IDU: Illegal drug user
- HBV: Hepatitis B virus
- HCV: Hepatitis C virus
- HDV: Hepatitis D virus

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Table 1. Anti-HDV positive group in YCTH; clinical and virological characteristics

Serial number	Gender	Age	*IDU	**Prostitution	Cirrhosis	Splenomegaly	Ascites	***Liver fibrosis stage	Hepatoma	HBeAg	HBV DNA (IU/ml)	HBV tx	Anti-HCV Antibody	HDV RNA (IU/ml)
1	**M**	**47**	＋	－	－	－	－	**F1**	－	－	**< 6**	－	＋	**< 21.2**
2	**M**	**68**	－	－	－	－	－	**F1**	－	－	**< 6**	－	－	**< 21.2**
3	**F**	**51**	－	－	－	－	－	**F1**	－	－	**< 6**	－	－	**< 21.2**
4	**M**	**49**	－	－	－	－	－	**F0**	－	－	**562**	－	－	**< 21.2**

- HBV tx: HBV patient under anti-viral treatment
- ＋: positive
- －: negative
- *IDU: History of intravenous drug use
- **Prostitution: exposure of prostitution
- ***Liver fibrosis stage was determinted by sonography with acoustic radiation force impulse imaging or fibrosis-4 score

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Table 2. Anti-HDV positive group in YCTH; biochemistry characteristics

Serial number	WBC (/uL)	Hb (g/dL)	platlet (1000/uL)	INR	AST (U/L)	ALT (U/L)	Bil-T (mg/dL)	Albumin (g/dL)	creatinine (g/dL)	AFP (ng/mL)
1	7.01	15.9	170	0.93	34	39	0.36	4.2	0.87	1.3
2	7.09	14.2	293	0.93	39	43	0.3	4	1.14	4.4
3	4.37	9.7	253	0.99	21	12	0.27	4.7	0.56	1.6
4	6.04	15.9	249	0.95	29	41	0.94	4.6	0.85	4.6

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Table 3. Anti-HDV positive group in NTUH; clinical and virological characteristics

Serial number	Gender	Age	*IDU	**Prostitute	Cirrhosis	Splenomegaly	Ascites	***Liver fibrosis stage	Hepatoma	HBeAg	HBV DNA (IU/ml)	HBV tx	Anti-HCV antibody	HDV RNA (IU/ml)
1	F	60	−	−	+	−	−	F1	−	−	8560	−	−	**< 21.2**
2	M	66	−	−	+	+	+	F4	−	−	< 6	+	−	**< 21.2**
3	M	55	−	−	+	−	−	F1	−	−	< 6	−	−	**< 21.2**
4	F	69	−	−	+	−	−	F4	−	−	117000	−	−	**< 21.2**
5	M	53	−	−	+	−	−	F1	−	−	< 6	+	−	**< 21.2**
6	M	67	−	−	+	−	−	F1	−	−	< 6	+	−	**< 21.2**
7	F	53	−	−	+	−	−	F1	−	−	< 6	+	−	**< 21.2**
8	M	51	−	−	+	−	−	F2	−	−	< 6	−	−	**< 21.2**
9	M	49	−	−	+	−	+	F2	−	+	< 6	+	−	**< 21.2**
10	F	62	−	−	+	+	−	F4	−	−	90500	−	−	**< 21.2**
11	M	66	−	−	+	+	−	F1	−	−	52600	−	−	82000

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Serial number	Gender	Age	*IDU	**Prostitution	Cirrhosis	Splenomegaly	Ascites	***Liver fibrosis stage	Hepatoma	HBeAg	HBV DNA (IU/ml)	HBV tx	Anti-HCV antibody	HDV RNA (IU/ml)
12	M	70	−	−	−	+	+	F4	+	−	< 6	+	−	**< 21.2**
13	M	53	−	−	+	−	−	F1	−	−	< 6	+	−	**< 21.2**
14	M	60	−	−	+	−	+	F1	−	−	< 6	+	−	**< 21.2**
15	M	58	−	−	+	−	−	F0	−	−	< 6	−	−	150
16	M	74	−	−	+	−	−	F3	−	−	< 6	+	−	
17	M	53	−	−	+	−	+	F3	−	+	< 6	+	−	
18	M	71	−	−	+	−	−	F1	−	−	24	−	−	

- HBV tx: HBV patient under anti-viral treatment
- ＋: positive
- －: negative
- *IDU: History of intravenous drug use
- **Prostitution: exposure of prostitution
- ***Liver fibrosis stage was determinted by sonography with acoustic radiation force impulse imaging or fibrosis-4 score

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Table 4. Anti-HDV positive group in NTUH; biochemistry characteristics

Serial number	WBC (/uL)	Hb (g/dL)	platlet (1000/uL)	INR	AST (U/L)	ALT (U/L)	Bil-T (mg/dL)	Albumin (g/dL)	creatinine (g/dL)	AFP (ng/mL)
1	5.08	12.6	230	NA	21	19	0.68	4.5	0.6	2.28
2	3.59	14.6	116	1.01	29	22	0.93	4.8	1.0	2.45
3	5.79	15.7	222	0.99	24	38	0.51	4.6	0.9	2.00
4	4.22	12.1	132	0.87	33	20	1.02	4.2	1.0	2.00
5	9.04	14.7	241	NA	33	40	0.73	4.6	1.2	2.00
6	5.59	15.1	246	1.03	18	14	0.88	4.5	0.8	2.00
7	5.66	13.1	211	1.01	23	16	0.49	4.5	0.7	5.61
8	7.32	14.1	160	0.98	68	147	0.59	4.4	0.9	3.22
9	6.23	14.2	124	1.05	26	31	0.71	4.4	1.0	3.40
10	4.86	13.3	121	1.19	51	56	0.47	3.9	0.6	3.50

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Serial number	WBC (/uL)	Hb (g/dL)	platlet (1000/uL)	INR	AST (U/L)	ALT (U/L)	Bil-T (mg/dL)	Albumin (g/dL)	creatinine (g/dL)	AFP (ng/mL)
11	3.99	9.8	201	1.21	24	34	0.55	3.6	11.2	2.00
12	3.66	13.1	83	1.3	78	77	1.21	4.1	1.1	17.49
13	7.71	16.1	202	NA	26	44	0.75	4.3	0.9	3.69
14	6.27	12.3	201	0.95	31	59	0.82	4.6	1.3	2.78
15	6.59	14.5	317	1.03	32	39	0.52	4.2	0.8	2.52
16	5.51	14.6	200	NA	32	36	0.94	4.3	NA	2.77
17	7.23	13.4	127	1.11	30	44	1.03	4.7	2.0	2.51
18	8.34	12.9	306	NA	38	60	0.47	4.8	1.1	2.23

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Table 5. Anti-HDV positive group versus anti-HDV negative group; clinical and virological characteristics

	Anti-HDV = Negative (N=342)	Anti-HDV = Positive (N=4)	Overall (N=346)	p-value*
Gender				
Female	165 (48.2%)	1 (25.0%)	166 (48.0%)	
Male	177 (51.8%)	3 (75.0%)	180 (52.0%)	
Age				
n	342	4	346	
Mean±Std	52.6 ± 11.1	53.8 ± 9.6	52.6 ± 11.1	
Cirrhosis				
No	312 (92.3%)	4 (100.0%)	316 (92.4%)	0.9854
Yes	26 (7.7%)	0 (0.0%)	26 (7.6%)	
Splenomegaly				
No	312 (94.3%)	4 (100.0%)	316 (94.3%)	0.9879
Yes	19 (5.7%)	0 (0.0%)	19 (5.7%)	
Ascites				
No	321 (97.0%)	4 (100.0%)	325 (97.0%)	0.9864
Yes	10 (3.0%)	0 (0.0%)	10 (3.0%)	
Liver fibrosis stage				
F0	35 (24.6%)	1 (25.0%)	36 (24.7%)	0.1899
F1	47 (33.1%)	3 (75.0%)	50 (34.2%)	
F2	21 (14.8%)	0 (0.0%)	21 (14.4%)	
F3	21 (14.8%)	0 (0.0%)	21 (14.4%)	
F4	18 (12.7%)	0 (0.0%)	18 (12.3%)	
Hepatoma				
No	329 (98.2%)	4 (100.0%)	333 (98.2%)	0.9887
Yes	6 (1.8%)	0 (0.0%)	6 (1.8%)	
HBeAg				
Negative	271 (92.8%)	4 (100.0%)	275 (92.9%)	0.9870
Positive	21 (7.2%)	0 (0.0%)	21 (7.1%)	
HBV tx				
Negative	299 (87.4%)	4 (100.0%)	303 (87.6%)	0.9886
Positive	43 (12.6%)	0 (0.0%)	43 (12.4%)	
Anti_HCV antibody				
Negative	183 (96.3%)	3 (75.0%)	186 (95.9%)	0.1019
Positive	7 (3.7%)	1 (25.0%)	8 (4.1%)	

*The calculation of p-value is based on the logistic regression model adjusted with gender and age.

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- HBV tx: HBV patient under anti-viral treatment

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Table 6. Odds ratio Estimation by Anti-HDV positive group versus anti-HDV negative group; clinical and virological characteristics

	Odds Ratio Estimate	Lower Confidence limit	Upper Confidence limit	p-value
Cirrhosis	<0.001	<0.001	>999.999	0.9854
Splenomegaly	<0.001	<0.001	>999.999	0.9879
Ascites	<0.001	<0.001	>999.999	0.9864
Liver fibrosis stage	0.278	0.041	1.885	0.1899
Hepatoma	<0.001	<0.001	>999.999	0.9887
HBeAg	<0.001	<0.001	>999.999	0.9870
HBV tx	<0.001	<0.001	>999.999	0.9886
Anti-HCV antibody	7.520	0.670	84.350	0.1019

*The calculation is based on the logistic regression model adjusted with gender and age.

- HBV tx: HBV patient under anti-viral treatment

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Table 7. Anti-HDV positive group versus anti-HDV negative group, biological characteristics

	Anti-HDV = Negative (N=342)	Anti-HDV = Positive (N=4)	Overall (N=346)	p-value*
WBC(1000/uL)				
n	151	4	155	
Mean±Std	7.0 ± 2.7	6.1 ± 1.3	7.0 ± 2.6	0.4275
Hb(g/dL)				
n	150	4	154	
Mean±Std	13.6 ± 1.8	13.9 ± 2.9	13.6 ± 1.9	0.9001
platlet(1000/uL)				
n	135	4	139	
Mean±Std	208.2 ± 64.2	241.3 ± 51.5	209.2 ± 63.9	0.2408
INR				
n	93	4	97	
Mean±Std	1.1 ± 1.0	1.0 ± 0.0	1.1 ± 1.0	0.6743
AST(U/L)				
n	339	4	343	
Mean±Std	28.6 ± 18.0	30.8 ± 7.7	28.6 ± 17.9	0.9165
ALT(U/L)				
n	340	4	344	
Mean±Std	31.9 ± 29.4	33.8 ± 14.6	31.9 ± 29.3	0.9605
Bil-T(mg/dL)				
n	131	4	135	
Mean±Std	0.8 ± 0.5	0.5 ± 0.3	0.8 ± 0.5	0.1480
Albumin(g/dL)				
n	76	4	80	
Mean±Std	4.0 ± 0.6	4.4 ± 0.3	4.0 ± 0.6	0.2177
creatinine(g/dL)				
n	271	4	275	
Mean±Std	0.8 ± 0.4	0.9 ± 0.2	0.8 ± 0.4	0.8750
eGFR				
n	218	4	222	
Mean±Std	97.5 ± 25.8	97.8 ± 22.1	97.5 ± 25.7	0.9494
AFP(ng/mL)				
n	333	4	337	
Mean±Std	25.5 ± 325.1	3.0 ± 1.8	25.2 ± 323.1	0.8389

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*The calculation of p-value is adjusted with gender and age. For the continuous response, the analysis of covariance is used.

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Table 8. National Taiwan University Hospital (NTUH) versus Yonghe Cardinal Tien Hospital (YCTH) of anti-HDV positive group; clinical and virological characteristics

	YCTH (N=4)	NTUH (N=18)	Overall (N=22)	p-value*
Gender				
Female	1 (25.0%)	4 (22.2%)	5 (22.7%)	
Male	3 (75.0%)	14 (77.8%)	17 (77.3%)	
Age				
n	4	18	22	
Mean±Std	53.8 ± 9.6	60.6 ± 7.8	59.3 ± 8.4	
Cirrhosis				
No	4 (100.0%)	14 (77.8%)	18 (81.8%)	0.9672
Yes	0 (0.0%)	4 (22.2%)	4 (18.2%)	
Splenomegaly				
No	4 (100.0%)	13 (72.2%)	17 (77.3%)	0.9632
Yes	0 (0.0%)	5 (27.8%)	5 (22.7%)	
Ascites				
No	4 (100.0%)	17 (94.4%)	21 (95.5%)	0.9663
Yes	0 (0.0%)	1 (5.6%)	1 (4.5%)	
Liver fibrosis stage				
F0	1 (25.0%)	1 (5.6%)	2 (9.1%)	0.1302
F1	3 (75.0%)	9 (50.0%)	12 (54.5%)	
F2	0 (0.0%)	2 (11.1%)	2 (9.1%)	
F3	0 (0.0%)	2 (11.1%)	2 (9.1%)	
F4	0 (0.0%)	4 (22.2%)	4 (18.2%)	
Hepatoma				
No	4 (100.0%)	17 (94.4%)	21 (95.5%)	0.9663
Yes	0 (0.0%)	1 (5.6%)	1 (4.5%)	
HBeAg				
Negative	4 (100.0%)	15 (83.3%)	19 (86.4%)	0.9568
Positive	0 (0.0%)	2 (11.1%)	2 (9.1%)	
HBV tx				
Negative	4 (100.0%)	8 (44.4%)	12 (54.5%)	0.9531
Positive	0 (0.0%)	10 (55.6%)	10 (45.5%)	
Anti_HCV antibody				
Negative	3 (75.0%)	18 (100.0%)	21 (95.5%)	0.9324
Positive	1 (25.0%)	0 (0.0%)	1 (4.5%)	

*The calculation of p-value is adjusted with gender, age, and hospital. For the

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continuous response, the analysis of covariance is used. For the category response, the logistic regression is used.

- HBV tx: HBV patient under anti-viral treatment

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Table 9. Odds ratio Estimation by National Taiwan University Hospital (NTUH) versus Yonghe Cardinal Tien Hospital (YCTH) of anti-HDV positive group; clinical and virological

	Odds Ratio Estimate	Lower Confidence limit	Upper Confidence limit	p-value
Cirrhosis	>999.999	<0.001	>999.999	0.9672
Splenomegaly	>999.999	<0.001	>999.999	0.9632
Ascites	>999.999	<0.001	>999.999	0.9663
Liver fibrosis stage	8.102	0.539	121.696	0.1302
Hepatoma	>999.999	<0.001	>999.999	0.9663
HBeAg	>999.999	<0.001	>999.999	0.9568
HBV tx	>999.999	<0.001	>999.999	0.9531
Anti-HCV antibody	0.195	<0.001	>999.999	0.9324

- HBV tx: HBV patient under anti-viral treatment

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Table 10. National Taiwan University Hospital (NTUH) versus Yonghe Cardinal Tien Hospital (YCTH) of anti-HDV positive group; biological characteristics

	YCTH (N=4)	NTUH (N=18)	Overall (N=22)	p-value*
WBC(1000/uL)				
n	4	18	22	
Mean±Std	6.1 ± 1.3	5.9 ± 1.6	6.0 ± 1.5	0.7615
Hb(g/dL)				
n	4	18	22	
Mean±Std	13.9 ± 2.9	13.7 ± 1.5	13.7 ± 1.7	0.9394
platlet(1000/uL)				
n	4	18	22	
Mean±Std	241.3 ± 51.5	191.1 ± 65.6	200.2 ± 65.2	0.1575
INR				
n	4	13	17	
Mean±Std	1.0 ± 0.0	1.1 ± 0.1	1.0 ± 0.1	0.2063
AST(U/L)				
n	4	18	22	
Mean±Std	30.8 ± 7.7	34.3 ± 16.0	33.6 ± 14.7	0.8865
ALT(U/L)				
n	4	18	22	
Mean±Std	33.8 ± 14.6	44.2 ± 30.8	42.3 ± 28.5	0.4408
Bil-T(mg/dL)				
n	4	18	22	
Mean±Std	0.5 ± 0.3	0.7 ± 0.2	0.7 ± 0.3	0.1191
Albumin(g/dL)				
n	4	18	22	
Mean±Std	4.4 ± 0.3	4.4 ± 0.3	4.4 ± 0.3	0.6383
creatinine(g/dL)				
n	4	17	21	
Mean±Std	0.9 ± 0.2	1.6 ± 2.5	1.5 ± 2.3	0.7891
eGFR				
n	4	17	21	
Mean±Std	97.8 ± 22.1	78.7 ± 27.7	82.4 ± 27.3	0.4328
AFP(ng/mL)				
n	4	18	22	
Mean±Std	3.0 ± 1.8	3.6 ± 3.6	3.5 ± 3.3	0.9950

*The calculation of p-value is adjusted with gender, age, and hospital. For the

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continuous response, the analysis of covariance is used. For the category response, the logistic regression is used.

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