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Full Length Article

The effect of chronic liver disease on venous thromboembolism among medically managed patients in Singapore General Hospital

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ABSTRACT

Background: Chronic liver disease (CLD) has been suggested to be associated with venous thromboembolism (VTE) in western populations. However, little is known about the risk effects of CLD on VTE among Asians.
Objective: To compute the prevalence of VTE among hospitalised Asian patients, and to evaluate the pattern and scale of risk effects of CLD on VTE occurrence.
Method: Retrospective study of hospital discharge database from 2004 to 2011 to identify patients with VTE and CLD using International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Australian Modification (ICD-9-AM) codes.
Results: Of 199904 medically managed inpatients during the 8 years, 1744 (0.9%) patients had VTE. Patients with CLD had significant higher prevalence of VTE (non-cirrhosis CLD 1.5%, cirrhosis 2.0%) than patients without CLD (0.8%, $p < 0.001$). In the logistic regression analyses, non-cirrhosis CLD (odds ratio, OR 1.4, 95% CI 1.2-1.7, $p < 0.001$) and cirrhosis (OR 1.5, 95% CI 1.2-2.0, $p = 0.002$) were significant predictors of VTE after adjustment for age, gender, ethnicity, hospital long stayer, cancer, infectious disease, and other comorbid conditions such as diabetic mellitus, anaemia, and cardiovascular, cerebrovascular, renal and pulmonary diseases.
Conclusion: CLD, particular liver cirrhosis, increases the risks of VTE in hospitalised Asian patients. As CLD patients are perceived to be at risks of bleeding due to the prolonged clotting times and thrombocytopenia, the results of this study brings attention to opposite end of the haemostatic pendulum in patients with chronic liver disease.

1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), is widely recognized as a major health hazzrd with substantial risk for reduced survival and considerable long-term morbidity and mortality [1,2]. The association of chronic liver disease (CLD) with VTE development is ambiguous. Markedly reduced risk (odds ratio, OR, 0.10) [3] or no association with chronic liver disease [4] have been reported in patients with VTE. On the other hand, increased risk has also been reported. In a large nationwide Danish case–control study, Sogaard et al. recruited approximately 99,000 patients with VTE, and found significantly increased risk of VTE among patients with CLD [5]. In the subgroup analysis, both cirrhotic liver disease and non-cirrhotic liver disease were significantly associated with VTE and the risk ratios (RR) were 1.74 and 1.87, respectively. However, in Asian population, there is scarce data addressing the risk effect of CLD on VTE thus far. In a recent propensity matched case control study of 2223 cirrhotic patients and 22 230 non-cirrhotic patients from Tai Wan, Ng et al. reported a much increased risk of VTE (OR 4.4, 95% CI 1.4–14.0), especially in patients with advanced cirrhosis [6].

Medical patients represent the majority of hospitalized patients, and an estimated 75% of fatal PE occurs in medical inpatients [2]. Recent epidemiologic studies estimate that approximately one-third of acute care hospital patients are at risk for developing VTE [7]. The American College of Chest Physicians (ACCP) have developed evidence-based recommendations regarding the prevention of VTE among hospitalised medical patients [8]. Unfortunately only half of the medical inpatients receive appropriate thromboprophylaxis [9,10]. In Asia, the awareness of the risk of VTE in medical patients and information about the associated prophylactic practices are scarce [10]. Moreover, there are no guidelines regarding DVT prophylaxis in hospitalised patients with liver disease. Thus, the aim of the study was to assess the prevalence of VTE in medically managed inpatients admitted to the largest tertiary care hospital in Singapore over an eight-year period, and to investigate the effect of CLD on VTE using hospital discharge database.

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2. Methods

2.1. Setting and Design

Singapore General Hospital (SGH) is the largest acute tertiary-care hospital in Singapore with 1775-beds, serving approximately one-third of the total population of Singapore [11], and managing approximately 80,000 in patients per year. Data from all hospitalised patients aged 18 years and above who were admitted into SGH from January 1, 2004 to December 31, 2011 were collected from the hospital's data warehouse at the Information Technology Department, SingHealth Group. Data included demographic information such as age, gender, ethnicity, clinical characteristics including hospital admission and discharge date, up to 10 International Statistical Classification of Diseases and Related Health Problems, 9th Revision, Australian Modification (ICD-9-AM) diagnosis codes, up to 10 ICD-9-AM procedure codes, discharge status, and disposition at discharge. The protocol for this study was approved by the Ethics Committee of the Singapore General Hospital. Informed consent was exempted as the study involved data retrieval from hospital database.

2.2. Case Definitions

Patients with VTE (DVT or PE), CLD and the various co-morbidities were identified using the discharge record with one or more of the 10 ICD-9-AM diagnostic and procedure codes as outlined in Table 1 [12]. Comorbidities and other risk factors including infection, pulmonary disease, renal disease, diabetes mellitus, cardiovascular disease, cerebrovascular disease, cancer and anaemia [13]. In order to adjusting the effect of hospital length of stay on the development of VTE, patients with a hospital stay of 21 days and above were arbitrarily defined as long stayer.

2.3. Validation of Diagnosis and Outcome

The predictive value of coding diseases compared to diagnoses confirmed by scrutiny of clinical records has been shown to be 90% for PE [5,14] and slightly lower for DVT and liver diseases [5,14,15]. We also validated the ICD-9-AM code for the identification of CLD and VTE by checking the medical records randomly selected from the electronic database in the year 2010 at our hospital. CLD and VTE were confirmed by imaging studies. Positive predictive value (PPV) was estimated. The diagnosis was confirmed by chart review in 48 of 50 randomly selected patients with codes for VTE, indicating a PPV of 96.0% (95% confidence interval [CI] 89.6–99.9%). Also, 50 randomly selected patients with codes for CLD, 49 were confirmed to have CLD, indicating a PPV of 98% (95% CI 93.0–99.8%).

2.4. Statistical Analysis

Categorical variables were reported as percentages, and continuous variables as mean and SD with the exception of hospital length of stay (LOS), where geometric mean (GM) and 95% confidence interval (CI) was used due to its skewed distribution. Patients with CLD and without CLD were compared using the Chi Square test. LOS was compared using the Mann–Whitney U test. Logistic regression was used to assess the association of VTE with CLD, adjusted for age, gender, ethnicity, long stayer, cancer, infectious disease, and other comorbid conditions such as diabetic mellitus, anaemia, cardiovascular, cerebrovascular, renal and pulmonary diseases. The Hosmer–Lemeshow chi-square goodness-of-fit tests were used for model building. The area under the receiver operating curve (ROC) is also presented for the final VTE model.

All tests were two sided, with p-values of $p < 0.05$ considered statistically significant. Data analysis was performed using STATA Version 12.0 (StataCorp, College Station, TX, USA).

Table 1
ICD-9-AM codes used to define chronic liver disease (CLD), VTE, comorbidities and other risk factors.

Non cirrhosis CLD	
Alcohol-related liver disease	571.1, 571.3
Alcohol use/abuse	291.0–291.4; 291.8–291.9; 303.0; 303.9; 305; 357.5; 425.5; 535.3; 790.3; 977.3; 980.0–980.1; V11.3; V70.4
Chronic hepatitis C virus infection	070.4–070.5; 070.7
Chronic hepatitis B virus infection	070.2–070.3
Disorders of iron metabolism	275.0; 285.0
Wilson's disease	275.1
∝ — 1-antitrypsin deficiency	277.6
Pregnancy/liver disease in pregnancy	V22; 645.1–645.11; 646.7
Gallbladder disease	575.9–575.11
Chronic hepatitis	571.4
Viral hepatitis	070.49; 070.59; 070.6; 070.9; 573.1–573.2
Chronic liver disease without alcohol	571.8–571.9
Other sequalae of chronic liver disease	456.0–456.1; 572.1–572.4; 567.2; 567.9; 570; 572.8; 573; 789.5
Abdominal ultrasound	88.74; 88.76
Abdominal computed tomography	88.01
Abdominal magnetic resonance imaging	88.97
Liver biopsy	50.0–50.9
Cirrhosis	
Cirrhosis	571.2, 571.5–571.6
VTE	
PE	415.1, 634.6, 635.6, 636.6, 637.6, 638.6, 673.2
DVT	451.1, 451.2, 451.9, 453.1, 453.2, 453.4, 453.8, 453.9, 444.21, 444.81, 671.3, 671.4, 671.9, 997.2
Comorbidities and other risk factors	
Pulmonary disease	487-519
Renal disease	580-593
Diabetes mellitus	250
Cardiovascular disease	410, 412, 428
Cerebrovascular disease	430-438
Cancer	140- 208
Anaemia	280-285
Infection	001-139.8, 480–486, 996.62

3. Results

Of 199904 medically managed hospitalised patients, 6372 (3.2%) patients had CLD. Characteristics of the patients are as listed in Table 2. Of note, a female predominance, fewer Malays and more co-morbidities, including a higher cancer rate, were seen in the CLD group.

As for clinical outcomes, CLD patients were more likely to be admitted to ICU (1.9% vs. 1.1%, $p < 0.001$), had longer length of hospital stay (geometric mean 3.6 vs. 2.3 days, $p < 0.001$), higher 30-day all-cause unscheduled readmission rate (14.6% vs. 10.4%, $p < 0.001$) and higher hospital mortality rate (4.3% vs. 1.3%, $p < 0.001$).

VTE was present in 1744 (0.9%) of 199904 medically managed inpatients. CLD had significantly higher prevalence of overall VTE (1.6% vs. 0.8%), DVT (1.1% vs. 0.7%) and PE (0.6% vs. 0.3%, all $p < 0.001$) compared with that of non-CLD controls. This increase is seen in both in cirrhosis group and non-cirrhosis group (VTE 2.0%, 1.5, and 0.8%, $p < 0.001$; DVT 1.7%, 1.0, and 0.7%, $p < 0.001$; and PE 0.5%, 0.6%, and 0.3%, $p = 0.001$; Table 3) respectively. This VTE risk remains elevated for CLD non-cirrhosis (OR 1.4, 95% CI 1.2-1.7, $p < 0.001$) and for CLD cirrhosis (OR 1.5, 95% CI 1.2-2.0, $p = 0.002$), even after adjustment using multivariate logistic regression analysis for other co-morbidities, as shown in Table 4.