Dig Dis Sci (2008) 53:3012–3017
DOI 10.1007/s10620-008-0265-3

ORIGINAL ARTICLE

Deep Vein Thrombosis and Pulmonary Embolism in Cirrhosis Patients

David Gulley · Evgenia Teal · Attaya Suvannasankha · Naga Chalasani · Suthat Liangpunsakul

Received: 27 November 2007 / Accepted: 26 March 2008 / Published online: 29 April 2008

Abstract *Background and Aims* It is a commonly held notion that patients with cirrhosis do not suffer from deep vein thrombosis (DVT) or pulmonary embolism (PE) because they are naturally anticoagulated. However, to date, no studies have been carried out that objectively address this issue. We conducted a study to examine the relationship between cirrhosis and DVT/PE events. *Methods* A case–control study of patients seen at a tertiary care hospital was performed. Cases were hospitalized patients with biopsy and/or imaging plus clinical evidence of cirrhosis. Well-matched patients with no known evidence of cirrhosis served as controls. The DVT/PE events were identified by the international classification of disease-9 (ICD-9) codes and confirmed with radiographic/nuclear imaging. The Charlson Index was calculated to determine the comorbidity. The incidence of DVT/PE in cirrhotic patients was also compared to patients with chronic kidney disease (CKD), congestive heart failure (CHF), and solid organ cancers. *Results* This study consisted of 963 cirrhotics and 12,405 controls. Both the incidence of DVT/PE (1.8 vs. 0.9%, $P = 0.007$) and Charlson Index scores (3.2 ± 1.8 vs. 0.9 ± 1.5, $P < 0.001$) were higher in cirrhotics than in the controls. However, in the multivariate analysis, the presence of cirrhosis was not associated with DVT/PE [odds ratio (OR) 0.87, $P = 0.06$]. Partial thromboplastin time (PTT; OR 0.88, $P = 0.04$) and serum albumin (OR 0.47, $P = 0.03$) were the independent predictors of DVT/PE. The incidence of DVT/PE in cirrhotics (1.8%) was lower than that in patients with other medical illnesses: 7.1% in CKD, 7.8% in CHF, and 6.1% in cancers. *Conclusion* Patients with cirrhosis do not have a lower risk of DVT/PE than non-cirrhotic controls without other significant co-morbidities, such as CHF, CKD, and solid organ cancers. Partial thromboplastin time and serum albumin were found to be independently predictive of DVT/PE in cirrhotic patients.

Keywords Cirrhosis · Deep vein thrombosis · Pulmonary embolism

D. Gulley · N. Chalasani · S. Liangpunsakul (✉)
Division of Gastroenterology and Hepatology, Indiana University Medical Center, 550 N. University Blvd, UH 4100, Indianapolis, IN 46202, USA
e-mail: sliangpu@iupui.edu

E. Teal
The Regenstrief Institute for Health Care, Indianapolis, IN, USA

A. Suvannasankha
Division of Hematology and Oncology, Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

S. Liangpunsakul
Roudebush Veterans Administration Medical Center, Indianapolis, IN, USA

Introduction

The endogenous coagulopathy in hospitalized cirrhosis patients is often considered to be protective against pulmonary thromboembolism (PE) and deep vein thrombosis (DVT) despite the lack of empirical data to validate this presumed low level of risk. A recent retrospective study examined 113 hospitalized cirrhosis patients with newly diagnosed PE/DVT and compared the results with those from an equal number of matched cirrhotic controls [1]. The findings of this study included a 0.5% incidence of newly diagnosed PE/DVT in cirrhotic patients and low serum albumin as an independent predictor of PE/DVT risk. Orthopedic or major surgery patients and those with underlying malignancies are examples of patient subsets

with a known increased risk of DVT/PE, and the incidence rate of PE/DVT in these groups of hospitalized patients has been reported to be between 4 and 12% [2]. This reported incidence was significantly higher than that reported by Northup et al. for their cirrhotic patients [1]. The pathogenesis of DVT/PE in cirrhotics is complex and can involve several of the following: concurrent co-morbidities which may precipitate a hypercoagulable state, limited physical activity due to the underlying chronic liver disease symptoms of massive ascites and/or lower extremity swelling [3], and acquired deficiencies in anti-coagulation factors [4]. These factors should be accounted for to fully evaluate the true risk of DVT/PE in these patients.

Given the lack of data in this area, we conducted the retrospective study reported here with the aim of (1) evaluating the incidence of DVT/PE in cirrhotic patients compared to well-matched controls without selected comorbidities who were hospitalized for DVT/PE and (2) assessing the incidence of DVT/PE in cirrhotic patients compared to matched controls with other co-morbidities that were known to increase the risk of DVT/PE (congestive heart failure (CHF), chronic kidney disease (CKD), and malignancies).

Methods

The study was reviewed and approved by the Institutional Review Board at the Indiana University School of Medicine and its affiliated hospitals. Data were collected and analyzed from the Regenstrief Medical Record system (RMRS). The system links five healthcare systems, including three major teaching hospitals on the Indiana University Medical Center campus (Indiana University Hospital, Wishard Memorial Hospital, and Riley Hospital for Children), 11 acute care hospitals, 13 homeless care sites, nearly 100 clinics/offices, and the county health departments in the state of Indiana. Data for more than 2 million patients, consisting of 300 million coded observations, 5.8 million text reports (including medical history, admission, and discharge summary, pathology reports, subspecialty clinic visit, and laboratory test results), 300,000 electrocardiogram tracings, in- and out-patient pharmacy prescription data, and 700,000 images, have been captured using a unique patient identifier [5]. A detailed description of this unique medical record system has been published elsewhere [6].

Patient Selections

This case–control study evaluated patients hospitalized in general medicine from January 1, 1995 to December 31, 2005 using the RMRS. Cases were identified by the appropriate international classification of diseases-9 (ICD-9) codes for cirrhosis (571.2, 571.5, 571.6, 571.8, 275.0, 275.1, 777.8), which had been diagnosed prior to or during the hospitalization. For confirmation of the cirrhosis diagnosis, cases *were also required* to have previous histories or clinical presentations of at least one of the followings: gastric/esophageal variceal bleed, presence of gastric/esophageal varices from the endoscopy report, hepatic encephalopathy, spontaneous bacterial peritonitis, liver biopsy proven cirrhosis, or imaging consistent with cirrhotic liver changes. The specific program within the RMRS system was used to link the subjects with the ICD-9 code for cirrhosis to the respective text reports of each particular individual during the patient data capturing process. To ensure that we included all potential subjects into the analyses, we also cross-referenced each patient to the ICD-9 and current procedural terminology codes (CPT) of the following diagnoses and/or procedures: variceal bleeding (571.5, 572.3), gastric varices (456.8), esophageal varices (456.1, 456.0, 571.5, 572.3), hepatic encephalopathy (572.2), spontaneous bacterial peritonitis (567.23), and liver biopsy (50.19, 50.11, 50.12) positive for cirrhosis. Another uniqueness of this software is that each subject is not counted twice. We subsequently linked the potential subjects to the in- and out-patient pharmacy prescription data. Those taking warfarin or enoxaparin *at the time of admission* were excluded. We next identified cases among cirrhotic patients who developed DVT/PE. The ICD-9 codes for PE (415.9, 415.11) and DVT (453.8, 451.11, 453.41, 453.0, 451.81, 453.40, 453.42, 453.9) were used to identify those cirrhosis patients with new onset PE/DVT during the hospital admission. *Subjects with a history* of PE/DVT prior to January 1, 1995 were excluded. Those patients who developed recurrent DVT/PE during the time of the study period were not re-counted. To make certain that we accurately identified subjects with DVT/PE, such diagnoses were confirmed by positive computerized tomography (CT) using the PE protocol, positive Doppler ultrasound of the extremities, and/or high probability V/Q scan.

There were two control groups in this study. The first control group consisted of patients with no known history of cirrhosis and selected comorbidities (CHF, CKD, or cancers) who were hospitalized during the study period. These patients were systematically matched to cirrhotic cases by age, race, and gender. We used the same method as described above to capture the diagnoses of DVT/PE in this control group. In order to compare the incidence of DVT/PE in cirrhotic patients to those with other co-morbidities, a second control group was identified. The subjects in this group were those with the following underlying diagnoses: (1) CHF (diagnosed by ICD-9 codes; 428, 428.9, 428.1, and/or by the echocardiogram report), (2) CKD (ICD-9 codes 586, 585.9, 639.3 2), or (3) malignancies (the four most common solid organ cancers in the USA: lung, breast, prostate, and colon

cancers [7]). The subjects in each sub-group were age-, gender-, race-, and Charlson Index (see below)-matched to those with cirrhosis.

Given the potential influence of co-morbidities on the occurrence of DVT and PE, we assessed the Charlson Index [8, 9] as a surrogate measurement for the burden of co-morbidities. The Charlson Index contains 19 categories of co-morbidity that are primarily defined using ICD-9-CM diagnoses codes (a few procedure codes are also employed). Each category has an associated weight based on the adjusted risk of 1-year mortality. A higher score indicates a more severe burden of co-morbidity. This index provides an objective measurement of co-morbid disease based on inpatient hospitalizations. A detailed description of this index and how to calculate it has been described elsewhere [8, 9].

Analysis

Statistical analysis was performed at the Regenstrief Institute for Health Care using SAS software (SAS Institute, Cary, N.C.). The descriptive statistics for the cases and controls, including means, standard deviations (SD), ranges, and percentages, were used to better characterize the two patient populations. The incidence of DVT/PE in each particular group was calculated by the number of new cases of DVT/PE diagnosed at admission or during hospitalization divided by the total number of subjects in each group who were hospitalized during the study period. Continuous and categorical variables were compared between groups using the Student t test and chi-square (χ^2) test, respectively. Univariate and multi-variate logistic regression analyses were performed to identify the predictors of DVT/PE in the study cohorts. In this study, those variables with the P value < 0.10 from the univariate analysis were then included as the independent variables in the multi-variate models. The strength of association was reported as the odds ratio (OR) and its corresponding 95% confident interval (95% CI). A P value < 0.05 was considered to be statistically significant.

Results

Comparison of the Incidence of DVT/PE in Cirrhotics Versus Non-cirrhotic Controls

During the study period, 963 cirrhotic cases (age 50.5 ± 11 years, females 32%, Caucasians 60%) and 12,405 controls without selected co-morbidities (age 50.5 ± 12 years, females 36%, Caucasians 60%) met criteria for inclusion in the study. Details on the demographics, baseline laboratory tests, Charlson Index, and the total events of DVT/PE in each group are shown in Table 1. The admission diagnoses for the control group were as follows: trauma, motor vehicle accidents, and skeletal fractures, 30%; burn, 20%; community-acquired pneumonia, 15%; psychiatric illnesses, 12%; gastrointestinal (GI)-related illnesses (acute appendicitis, acute pancreatitis, acute cholecystitis), 9%; obstetrics/gynecology-related issues, 7%; ophthalmologic problems, 1%; others, 6%. The incidence of DVT/PE in patients with cirrhosis and those without cirrhosis was 1.87 and 0.98%, respectively (OR 1.78, 95% CI 1.1–2.2, $P = 0.007$). As expected, the Charlson Index in the cirrhotic group was significantly higher than that in the non-cirrhotic patients (3.2 ± 1.9 vs. 0.96 ± 1.5, $P < 0.001$). To

Table 1 Selected demographics and characteristics of individuals with cirrhosis and controls without selected co-morbidities

Demographics and characteristics	Cirrhosis ($n = 963$)	Non-cirrhosis controls ($n = 12{,}405$)	P value
Age (years)	50.5 ± 11	50.5 ± 12	0.33
Female (%)	32	36	0.20
Caucasian (%)	60	60	0.87
Etiology of liver diseases (%)			
Hepatitis C	47.5%		
Alcohol	20.8%		
Cryptogenic	18.7%		
Hepatitis B	6.4%	2.5%	
Others	6.6%		
Cases with diagnosis of DVT/PE (%)	18 (1.87%)	121 (0.98%)	0.008
Charlson Index	3.2 ± 1.9	0.96 ± 1.5	0.001
Hemoglobin (g/dL)	10.9 ± 2.8	13.2 ± 2.4	0.001
Platelet counts ($\times 10^3/mm^3$)	144 ± 86	254 ± 104	0.001
INR	1.7 ± 2.1	1.1 ± 0.7	0.001
PTT (s)	35.8 ± 18	30.4 ± 14	0.001
T. Bilirubin (mg/dL)	3.9 ± 4.9	0.8 ± 1.2	0.001
AST (IU/L)	136 ± 218	78 ± 149	0.001
ALT (IU/L)	70 ± 143	71 ± 171	0.58
Albumin (g/dL)	2.7 ± 0.6	3.7 ± 0.6	0.001
T. protein (g/dL)	6.9 ± 1.1	7.1 ± 1.0	0.01
Blood urea nitrogen (mg/dL)	20.8 ± 20.5	17.7 ± 16.7	0.002
Creatinine (mg/dL)	1.3 ± 1.0	1.2 ± 0.5	0.74
Child-Pugh Score	8.2 ± 2.2	N/A	
Child classification (% cases)			
A	30	N/A	
B	65		
C	5		

Descriptive statistics are given in percentages or as the mean ± standard deviation

INR, International Normalized Ratio; PTT, partial thromboplastin time; AST, Aspartate aminotransferase; ALT, alanine aminotransferase; DVT, deep vein thrombosis; PE, pulmonary embolism

Table 2 Factors associated with DVT/PE in the entire study cohort ($n = 13,368$)

Factors associated with DVT/PE	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Presence of cirrhosis	1.93 (1.17–3.18)	0.001	0.86 (0.28–2.63)	0.06
Charlson Index	0.89 (083–0.96)	0.003	0.93 (0.74–1.16)	0.44
Hemoglobin (g/dL)	1.08 (1.01–1.15)	0.02	0.83 (0.70–1.00)	0.06
INR	0.92 (0.85–0.98)	0.02	1.03 (0.46–2.30)	0.95
PTT (s)	0.89 (0.87–0.97)	0.04	0.88 (0.84–0.94)	0.04
Albumin (g/dL)	0.36 (0.29–0.42)	0.001	0.47 (0.23–0.93)	0.03
Platelet counts (cells/mm^3)	1.00 (0.99–1.01)	0.50	–	–
Total bilirubin (mg/dL)	0.99 (0.91–1.07)	0.78	–	–
AST (IU/L)	1.00 (0.99–1.01)	0.57	–	–
ALT (IU/L)	1.00 (0.98–1.01)	0.31	–	–
Blood urea nitrogen (mg/dL)	0.99 (0.98–1.00)	0.17	–	–
Creatinine (mg/dL)	0.97 (0.88–1.08)	0.64	–	–

OR, Odds ratio; 95% CI, 95% confidence interval

determine whether the presence of cirrhosis is an independent predictor for DVT/PE, multi-variate analysis was performed to control for other potential confounders, such as Charlson Index and International Normalized Ratio (INR). The Charlson Index score (OR 0.93, 95% CI 0.74–1.16) and presence of cirrhosis (OR 0.87, 95% CI 0.2–2.6) were not independently associated with DVT/PE. Partial thromboplastin time (PTT) (OR 0.88: 95% CI 0.84–0.94) and serum albumin (OR 0.47, 95% CI 0.23–0.93) were the independent predictors of DVT/PE in this study cohort (Table 2). We also compared the risk of DVT/PE between compensated (Child A) and decompensated (Child B/C) cirrhotic patients and found that the incidence of DVT/PE in Child B/C and in Child A was 2.6 and 0.8%, respectively. Although, there was the trend towards the higher incidence of DVT/PE in decompensated cirrhotic patients ($P = 0.10$), the difference was not statistically significant.

Comparison of the Incidence of DVT/PE in Cirrhotics Versus Other Co-Morbid Illnesses

We next compared the incidence of DVT/PE in cirrhotic patients to age-, gender-, race-, and Charlson index-matched controls with underlying co-morbid illnesses. The detailed demographic data and the incidence of DVT/PE in each subgroup are shown in Table 3. The incidence of DVT/PE in subjects with cirrhosis (1.87%) was significantly lower than that in patients with CKD (7%; OR 0.25, 95% CI 0.15–0.41), CHF (7.75%; OR 0.23, 95% CI 0.14–0.37), and cancer (6.1%; OR 0.29, 95% CI 0.17–0.52). Figure 1 summarizes the odds ratio for the risk of developing DVT/PE when we used the incidence of DVT/PE in non-cirrhotic controls as a baseline reference.

Discussion

The results of our study demonstrate that hospitalized cirrhotic patients did not have a lower risk of DVT/PE than the appropriately matched non-cirrhotic controls without selected co-morbidities. However, the risk of developing DVT/PE was low when compared to age-, gender-, race-, and Charlson Morbidity index-matched subjects with other co-morbid illnesses that are well-known risk factors for DVT/PE [10].

The underlying coagulopathy in patients with cirrhosis has led to the assumption that these patients may be at a lower risk for developing DVT/PE. However, this perception is contrary to the results of several studies that have

Table 3 Selected demographics and characteristics of individuals with cirrhosis and controls with selected co-morbid illnesses

	Cirrhosis ($n = 963$)	Subjects with chronic renal failure ($n = 1692$)	Subjects with congestive heart failure ($n = 4489$)	Subjects with cancers ($n = 673$)	*P* value
Age (year)	50.5 ± 11	55 ± 12	50.0 ± 11	50 ± 9.7	0.45
Female (%)	32	40	36	40	0.10
Caucasian (%)	60	62	58	54	0.34
Charlson Index	3.2 ± 1.9	2.0 ± 1.4	2.2 ± 1.0	3.0 ± 1.6	0.26
Cases with diagnosis of DVT/PE (%)	18 (1.87%)	120 (7.0%)	348 (7.75%)	41 (6.1%)	<0.05

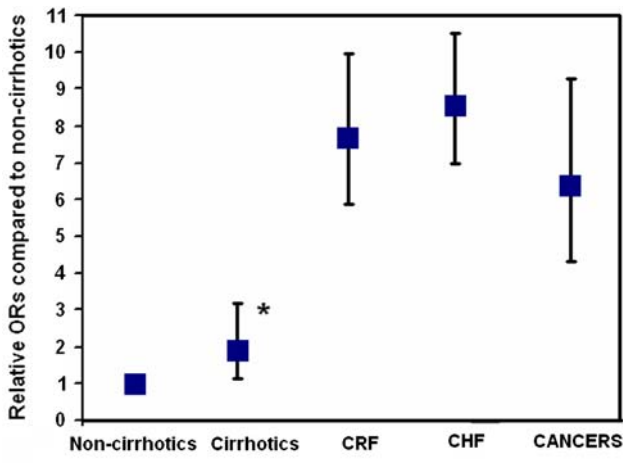

Fig. 1 The incidence of deep vein thrombosis/pulmonary embolism (DVT/PE) [reported as odds ratio (*OR*) and 95% confidence intervals] was significantly lower in cirrhotic patients than in patients with other medical illnesses. Although the incidence of DVT/PE was higher in cirrhotics when compared to non-cirrhotic controls, the difference was not significant in the multivariate analysis. *CRF* Chronic renal failure, *CHF* congestive heart failure. $*P = 0.06$

shown an increase in thromboembolic risk in cirrhotic patients [11]. Although the levels of several coagulation factors are low in cirrhosis patients [12], they also develop acquired deficiencies in the anti-coagulation factors (including protein C, protein S, and anti-thrombin III) [13]. Additionally, these patients often suffer from physical conditions which prohibit active lifestyles, thus perpetuating the risk of thromboembolism. Taken together, the pathogenesis of DVT/PE in cirrhotic patients is complex, with several factors involved, leading to the inconsistency in the reported incidence of DVT/PE in these patients [1, 10].

We found that underlying cirrhosis did not reduce risk of DVT/PE when cirrhotic patients were compared to non-cirrhotic patients without other co-morbidities. Our results are in accordance with that reported by Northup et al. [1]; however, several issues deserved further discussion. First, the risk of DVT/PE reported by Northup et al. was 0.5% compared to the 1.8% obtained in this study. The difference in the incidence rate relative to controls is likely due to the use of different control groups; cirrhotic patients without DVT/PE in the former and non-cirrhotic patients in the latter. Another possibility could be the manner in which the incidence rate was calculated. The denominator of our incidence rate was the number of cirrhotic subjects hospitalized during the study period; in the report by Northup et al. [1], the authors used the total inpatient cases who were hospitalized during the study period, using those without cirrhosis as their denominator. Second, we also found that serum albumin was an independent predictor for DVT/PE in cirrhotic patients. Because albumin is exclusively synthesized in the liver, low levels of serum albumin may serve as a marker for poor hepatic reserve. As such, these patients are likely to have deficiencies of anti-coagulation factors, thus placing them at risk for DVT/PE [1].

The findings that the incidence of DVT/PE in cirrhotic patients is much lower than that in subjects with other medical illnesses deserve further consideration. The reported incidence of DVT/PE in patients with CHF in our study is similar to that found in the recently published report based on the use of General Practice Research Database (GPRD), the computerized patient care system in the UK. However, the incidence of DVT/PE in chronic liver disease and cancer patients was reported to be 0.6 and 16%, respectively, in that study. Such differences may be attributed to the following reasons. First, we only studied patients with the five most common cancer diagnoses in the USA. Therefore, we did not include any hematological malignancies or other gastrointestinal cancers in the analysis. Second, the study based on the GPRD simply looked at the risk of thromboembolism in patients with chronic liver disease. In comparison, our inclusion criteria for cirrhosis may lead to the selection of more advanced liver disease cases. The risk of DVT/PE in cirrhotics in our study is higher. This correlates with studies showing that the thrombotic condition worsens as the liver disease progresses [11, 14]. Regardless of the reported incidence, the results from these two studies are in agreement that the risk of DVT/PE in cirrhosis is significantly lower than that in patients with CHF or cancers.

This study suffers from multiple inherent weaknesses. First, this is a retrospective study utilizing an electronic medical record system. Thus, it has the shortcoming of any retrospective study design. To overcome this issue, we have carefully selected the subjects with cirrhosis by cross-referencing with sign/symptoms of portal hypertension and/or decompensated liver diseases. Additionally, we have aggressively verified cases with DVT/PE, not only from the ICD-9 diagnosis, but also from the text reports and 'accepted standard diagnostic procedures (V/Q scan, CT scan of the chest with specific PE protocol)' in order to ensure that we did not over-estimate and recruit non-DVT/PE cases in the analyses. Second, as previously mentioned, we have developed rigorous criteria to identify cirrhotic cases. The result of utilizing these criteria could lead to a selection bias for more advanced cirrhotic patients; this would result in the inclusion of cases having a higher prevalence of confounding features, such as refractory ascites and limited physical activity. With this in mind, we carefully controlled for co-morbidity using the Charlson Index in the analyses. Finally, when a study is conducted to examine a disease/condition with a low incidence rate (such as the incidence of DVT/PE in cirrhosis), an essential requirement is that the sample size is large enough to avoid type II error (β error). In other words, this is the error of failing to observe a difference when in truth there is one.

However, given the strength of the RMRS database, we believe that we were able to capture a large number of subjects and eliminate this type of statistical error from our analyses.

In conclusion, we did not find a reduced risk of DVT/PE in cirrhotic patients when these were compared to non-cirrhotic controls, although this risk is much lower in the former than in patients with other co-morbid illnesses, such as CHF and malignancy. We also found that serum albumin and PTT were independent predictors of DVT/PE in the cirrhotic cohorts of our study. Our findings should alert healthcare providers to consider DVT/PE in the differential diagnosis when cirrhotic patients present with signs and symptoms compatible with venous thromboembolism.

References

1. Northup PG, McMahon MM, Ruhl AP, Altschuler SE, Volk-Bednarz A, Caldwell SH, Berg CL (2006) Coagulopathy does not fully protect hospitalized cirrhosis patients from peripheral venous thromboembolism. Am J Gastroenterol 101:1524–1528. doi:10.1111/j.1572-0241.2006.00588.x
2. Schrecengost JE, LeGallo RD, Boyd JC, Moons KG, Gonias SL, Rose CE Jr, Bruns DE (2003) Comparison of diagnostic accuracies in outpatients and hospitalized patients of D-dimer testing for the evaluation of suspected pulmonary embolism. Clin Chem 49:1483–1490. doi:10.1373/49.9.1483
3. Stanca CM, Bach N, Krause C, Tandon N, Freni MA, Gutierrez JA, Bodian C, Lopez J, Berk PD, Bodenheimer HC Jr., Branch AD, Odin JA (2005) Evaluation of fatigue in U.S. patients with primary biliary cirrhosis. Am J Gastroenterol 100:1104–1109. doi:10.1111/j.1572-0241.2005.41315.x
4. Jackson MR (1998) Diagnosis and management of venous thrombosis in the surgical patient. Semin Thromb Hemost 24[Suppl 1]:67–76
5. Overhage J, McDonald CJ, Suico JG (2000) The Regenstrief Medical Record System 2000: expanding the breadth and depth of a community wide EMR. Proc AMIA Symp 1173
6. McDonald CJ, Overhage JM, Tierney WM, Dexter PR, Martin DK, Suico JG, Zafar A, Schadow G, Blevins L, Glazener T, Meeks-Johnson J, Lemmon L, Warvel J, Porterfield B, Warvel J, Cassidy P, Lindbergh D, Belsito A, Tucker M, Williams B, Wodniak C (1999) The Regenstrief Medical Record System: a quarter century experience. Int J Med Inform 54:225–253. doi:10.1016/S1386-5056(99)00009-X
7. American Cancer Society (2007) Cancer facts and figures 2007. Database online. American Cancer Society, Altlanta. Accessed 18 Jan 2007
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383. doi:10.1016/0021-9681(87)90171-8
9. Charlson ME, Sax FL, MacKenzie CR, Braham RL, Fields SD, Douglas RG Jr (1987) Morbidity during hospitalization: can we predict it? J Chronic Dis 40:705–712 doi:10.1016/0021-9681(87)90107-X
10. Huerta C, Johansson S, Wallander MA, Garcia Rodriguez LA (2007) Risk factors and short-term mortality of venous thromboembolism diagnosed in the primary care setting in the United Kingdom. Arch Intern Med 167:935–943. doi:10.1001/archinte.167.9.935
11. Calmus Y, Robert A (1992) Increased procoagulant activity in peripheral blood mononuclear cells from patients with liver cirrhosis. Thromb Res 68:103–108. doi:10.1016/0049-3848(92)90132-T
12. Orlando M, Casalbore P, Camagna A, Lauro R, Tardella L, Hassan HJ (1982) Factor VII in liver cirrhosis. Haemostasis 11:73–78
13. Castelino DJ, Salem HH (1997) Natural anticoagulants and the liver. J Gastroenterol Hepatol 12:77–83. doi:10.1111/j.1440-1746.1997.tb00351.x
14. Zurborn KH, Kirch W, Bruhn HD (1988) Immunological and functional determination of the protease inhibitors, protein C and antithrombin III, in liver cirrhosis and in neoplasia. Thromb Res 52:325–336. doi:10.1016/0049-3848(88)90073-4