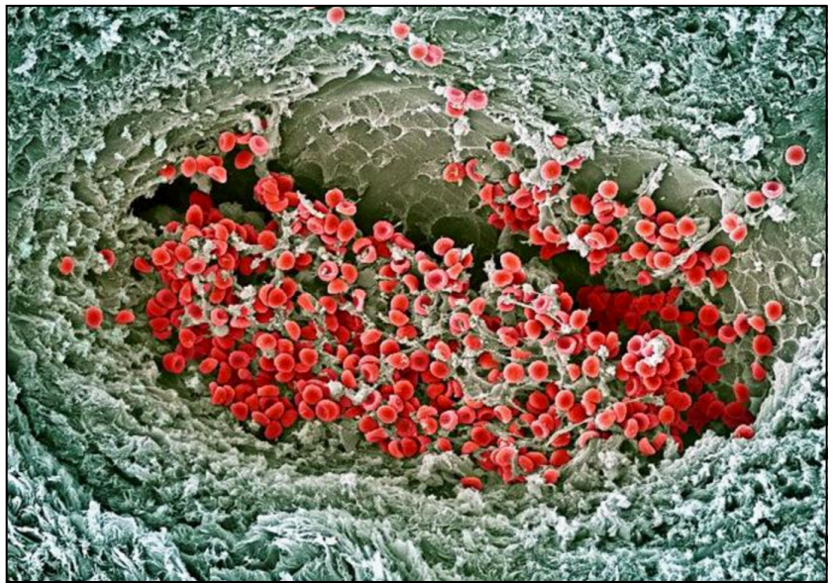
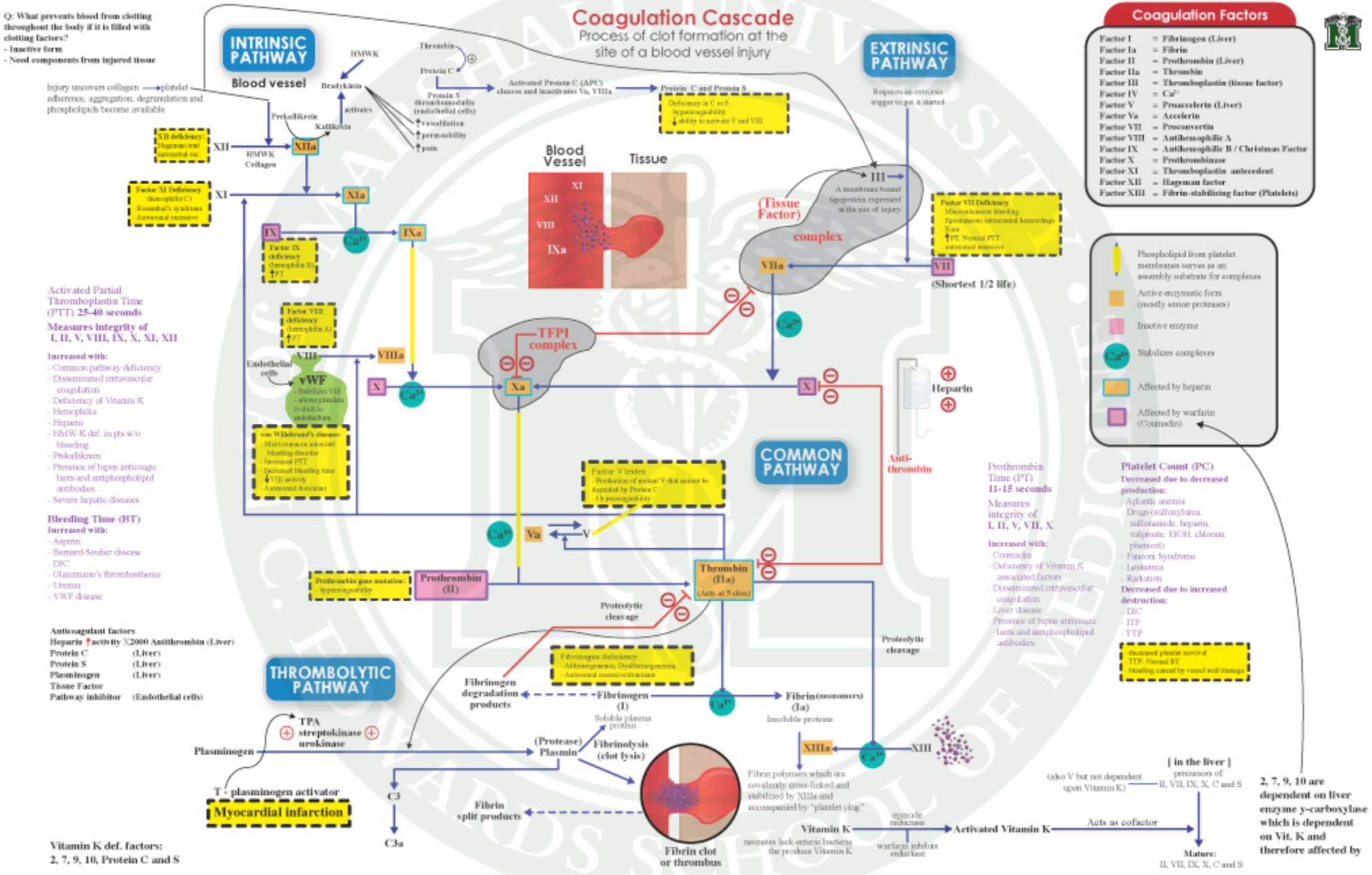
Liver Disease & Venous Thromboembolism



Does it really de(liver) less risk?

Ernest Law, BSc (Pharm), ACPR
Doctor of Pharmacy Student, Class of 2014
Faculty of Pharmaceutical Sciences, University of British Columbia
Ernest.Law@alumni.ubc.ca

"Of course we should order some VTE prophylaxis for this patient…wait, what's their INR? Elevated?! Never mind, they're **AUTO-ANTICOAGULATED**…"



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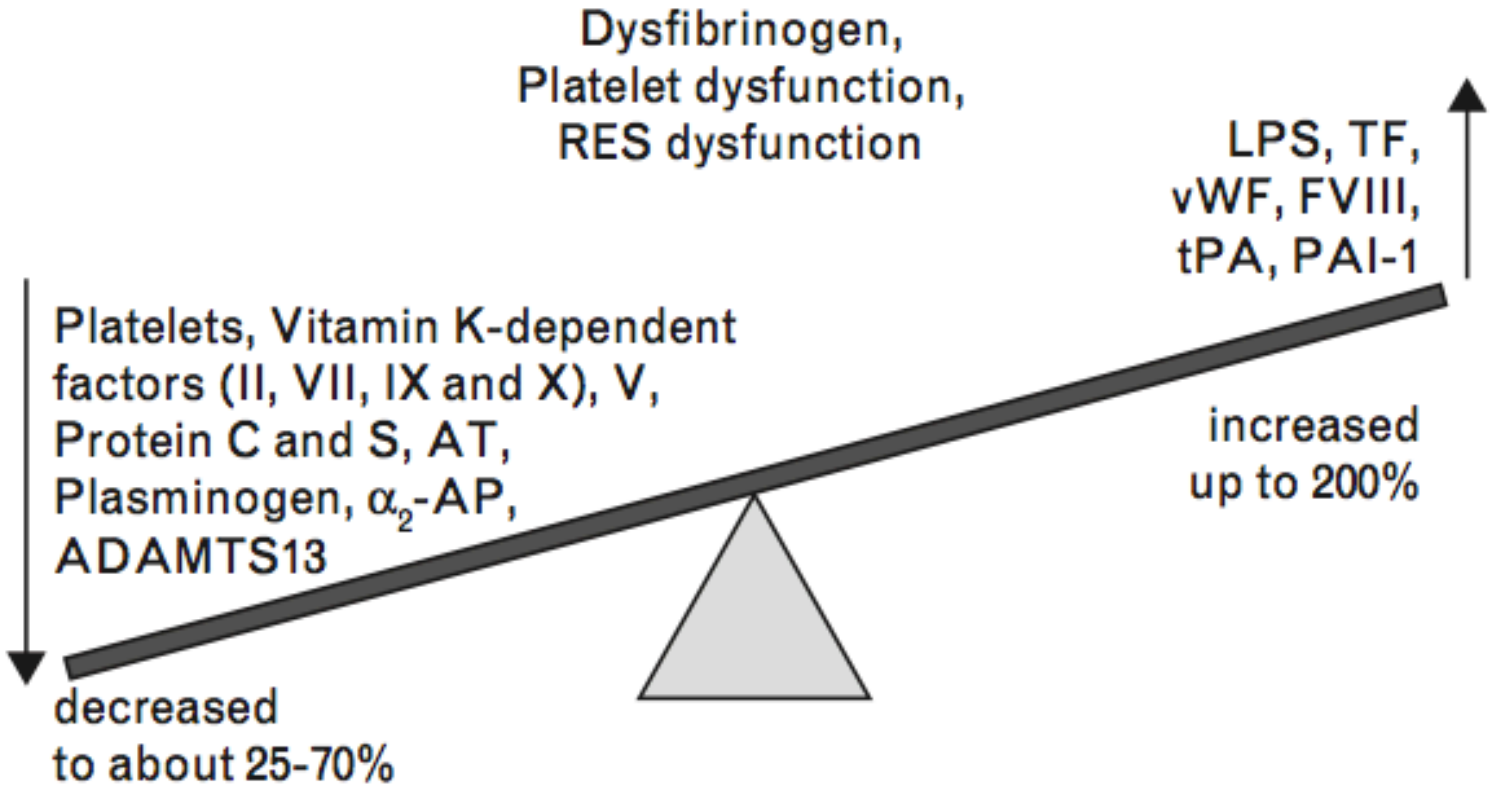
Pathophysiology



Low level balance →

high risk of bleeding and thrombosis!

Curr Opin Crit Care 2013, 19:142–148

Prothrombin Time & International Normalized Ratio (INR)

- Factors I, **II**, V, **VII** and **X**
- Not sensitive to intrinsic pathway factors (VIII, **IX**, XI, XII, XIII)
- Does not assess levels of protein C&S, antithrombin and von Willebrand
- Not intended to gauge coagulation status outside of pharmacologic therapy

Curr Opin Crit Care 2013, 19:142–148

CHEST 2012 VTE prophylaxis guidelines

Table 3—*Independent Risk Factors for Bleeding in 10,866 Hospitalized Medical Patient*[10]

Risk Factor[a]	Total Patients, No. (%) (N = 10,866)	OR (95% CI)
Active gastroduodenal ulcer	236 (2.2)	4.15 (2.21-7.77)
Bleeding in 3 mo before admission	231 (2.2)	3.64 (2.21-5.99)
Platelet count < 50 × 10^9/L	179 (1.7)	3.37 (1.84-6.18)
Age ≥ 85 y (vs < 40 y)	1,178 (10.8)	2.96 (1.43-6.15)
Hepatic failure (INR > 1.5)	219 (2.0)	2.18 (1.10-4.33)
Severe renal failure (GFR < 30 mL/min/m^2)	1,084 (11.0)	2.14 (1.44-3.20)
ICU or CCU admission	923 (8.5)	2.10 (1.42-3.10)
Central venous catheter	820 (7.5)	1.85 (1.18-2.90)
Rheumatic disease	740 (6.8)	1.78 (1.09-2.89)
Current cancer	1,166 (10.7)	1.78 (1.20-2.63)
Male sex	5,367 (49.4)	1.48 (1.10-1.99)

Data shown were obtained by multiple logistic regression analysis for characteristics at admission independently associated with in-hospital bleeding (major bleeding and clinically relevant nonmajor bleeding combined). GFR = glomerular filtration rate; INR = international normalized ratio.
[a]Although not specifically studied in medical patients, one would also expect dual antiplatelet therapy to increase the risk of bleeding.

CHEST 2012; 141(2)(Suppl):e195S–e226S

Clinical Question

Is the INR a useful parameter for assessing the benefit of VTE prophylaxis in hospitalized adult patients with liver disease?

Search Strategy

Search terms	Venous thromboembolism (VTE), deep vein thrombosis (DVT), prophylaxis, cirrhosis, liver disease, liver failure, chronic liver disease, coagulopathy
Databases	Google Scholar, MEDLINE, EMBASE, IPA, WHO ICTRP
Limits	Adults, English, Fully published text

Search Results

RCTs	**None; none upcoming**
Cohort	*Wu et al.* *Aldawood et al.* **Barclay et al.**
Case-control	**Northup et al.** **Gulley et al.** *Sogaard et al.*
Cross-sectional	**Edwards et al.**

Northup et al. (2006)

D	Retrospective case–control; 1993-2001
P	N=113 inpatients with cirrhosis (by liver biopsy or history) and newly diagnosed VTE; occurrence of VTE (doppler, CT angiography or direct imaging) Excluded: CVC releated thrombosis, portal/splenic/mesenteric vein thrombosis, prior history of PE or DVT, transplantation during admission, on anticoagulation
I	N=113 controls with cirrhosis but without VTE (matched by age, sex, race, cancer and other co-morbidities, and surgical procedures performed)
E	Risk factors associated with VTE
S	Multivariate conditional logistic regression analyses

Am J Gastroenterol. 2006; 101:1524-8.

Northup et al. (2006)

Table 3. Laboratory Characteristics of Case and Control Populations

(95% CI of mean) [Interquartile range]	Cirrhosis Patients with VTE, Cases (N = 113)	Cirrhosis Patients without VTE, Controls (N = 113)	*p*-Value
Admission MELD score*	11.5 (9.7–13.2) [3.5–17.9]	12.6 (10.8–14.4) [5.4–18.8]	0.35
Albumin g/dL	2.85 (2.70–3.01) [2.2–3.3]	3.10 (2.96–3.23) [2.6–3.7]	0.01
Total bilirubin mg/dL	2.10 (1.55–2.65) [0.7–2.7]	3.58 (2.59–4.56) [0.7–4.3]	0.14
International normalized ratio (INR)	1.40 (1.34–1.46) [1.2–1.5]	1.47 (1.38–1.55) [1.2–1.5]	0.50
Creatinine mg/dL	1.81 (1.44–2.19) [0.9–1.9]	1.50 (1.22–1.77) [0.8–1.5]	0.21
Platelet count $\times 10^3/\mu L$	198 (175–222) [112–263]	170 (149–192) [84–234]	0.08

Laboratory values are expressed as mean with 95% confidence interval. The interquartile range is expressed in brackets.
*Model for end-stage liver disease score = 11.2 ln(INR) + 3.78 ln(total bilirubin) + 9.57 ln(creatinine) + 6.43.

28.5 g/L vs. 31 g/L
(difference of 2.5 g/L)

Am J Gastroenterol. 2006; 101:1524-8.

Northup et al. (2006)

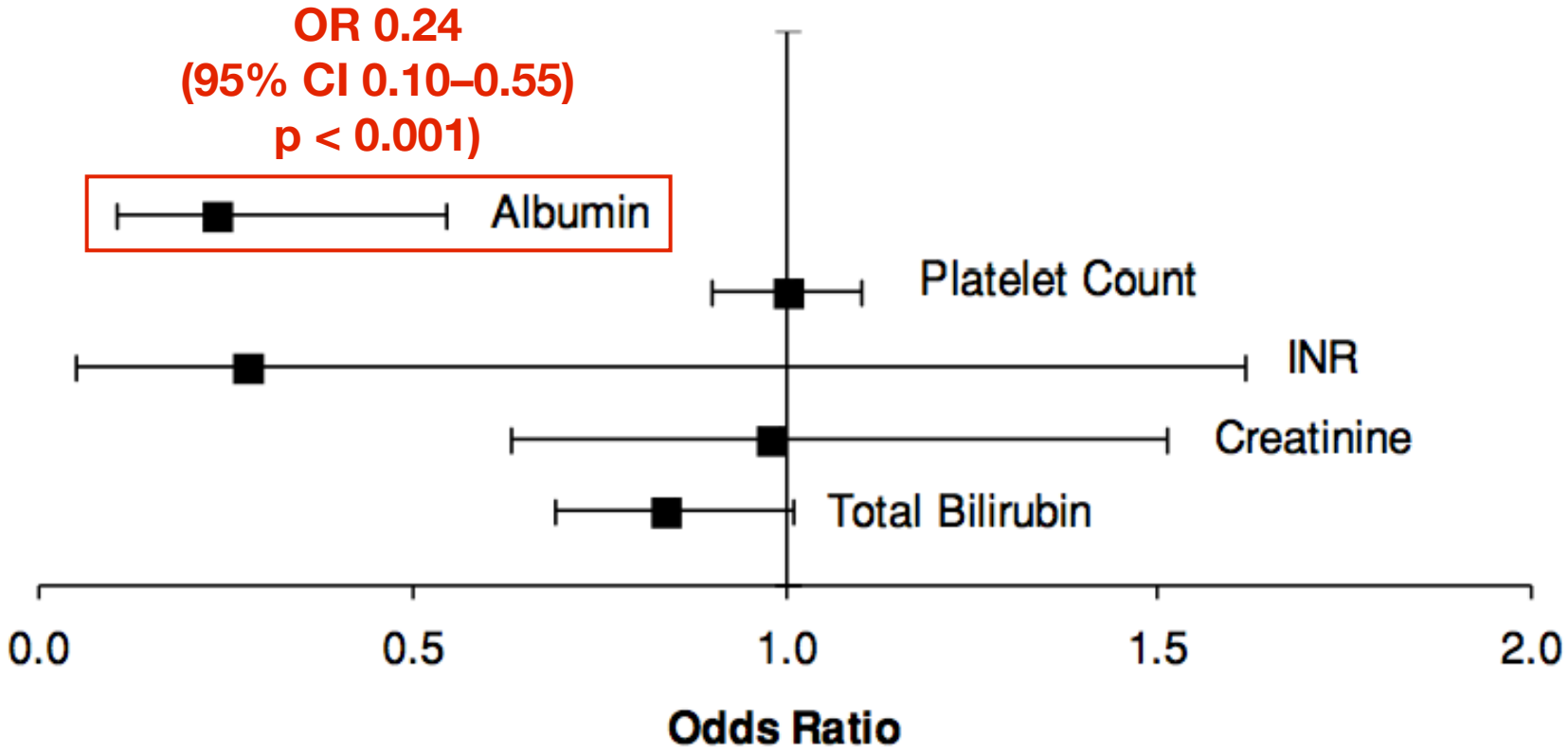


Figure 1. Odds ratios of laboratory predictors of VTE with upper and lower 95% confidence limits. Odds ratios are based on conditional logistic regression multivariate model. All odds ratios confidence intervals cross 1.0 except albumin.

Am J Gastroenterol. 2006; 101:1524-8.

Northup et al. (2006)

- "*Low serum albumin was strongly predictive of increased risk for developing VTE*"

Am J Gastroenterol. 2006; 101:1524-8.

Northup et al. (2006)

Strengths	• Appropriate to use case-control given low VTE rate • Reasonable matching parameters • Evaluates of relationships between various lab parameters
Limitations	• Small, retrospective design (type II error) • Albumin = acute phase reactant • Difficult to interpret magnitude of risk with albumin • Utility of pharmacologic prophylaxis?

Gulley et al. (2008)

D	Retrospective case-control study; 1995-2005
P	N=963 cases: hospitalized patients with cirrhosis and at least 1 presentation/history of complication Excluded: patients receiving anticoagulation
I	N=12,405 controls: patients without cirrhosis; two analyses +/- significant morbidities
E	Frequency of VTE in cirrhosis vs. Non-cirrhotic patients Indicators of higher VTE rates
S	Univariate and multivariate logistic regression analyses OR with 95% CI

Dig Dis Sci (2008) 53:3012–3017

Gulley et al. (2008)

Frequency of VTE: 1.87% (cirrhosis) vs. 0.98% (no cirrhosis)
P=0.007

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

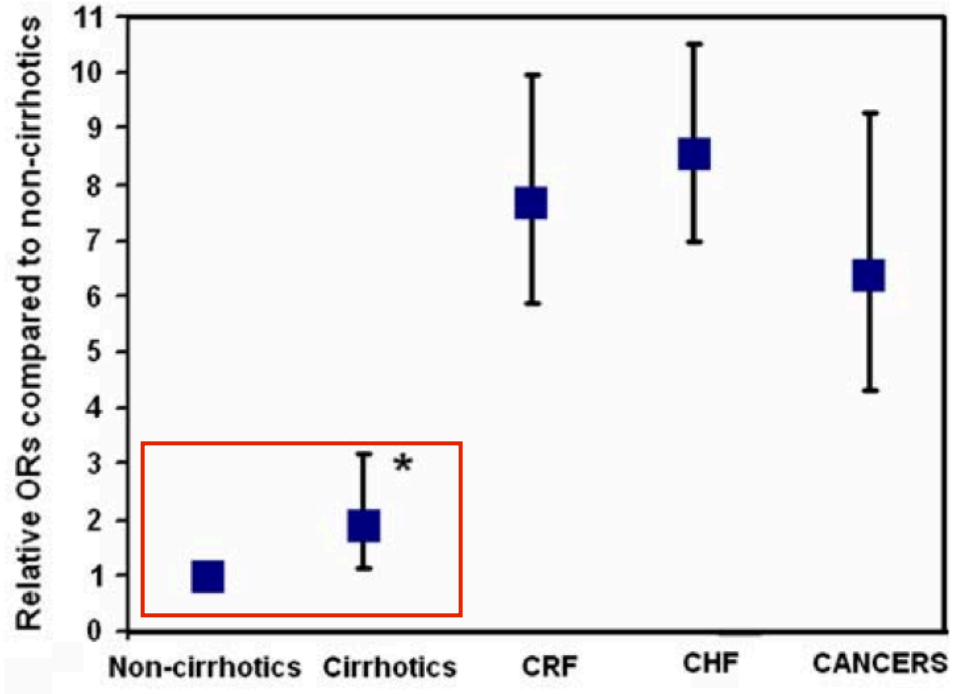
PTT (OR 0.88)
Albumin (OR 0.47)

Dig Dis Sci (2008) 53:3012–3017

Gulley et al. (2008)

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



Dig Dis Sci (2008) 53:3012–3017

Gulley et al. (2008)

- "*Patients with cirrhosis do not have a lower risk of DVT/PE than non-cirrhotic controls without other significant co-morbidities...*"
- *"...PTT and serum albumin were found to be independently predictive of DVT/PE..."*

Dig Dis Sci (2008) 53:3012–3017

Gulley et al. (2008)

Strengths	• Appropriate to use case-control given low VTE rate • Reasonable matching parameters • Evaluated impact of co-morbidities in patients with cirrhosis
Limitations	• Small, retrospective design • Albumin as acute phase reactant • Does not assess utility of pharmacologic prophylaxis

Dabbagh et al. (2010)

D	Retrospective chart review; 2000-2007
P	N=190 hospitalized adult patients with chronic liver disease (alcoholic, viral, cryptogenic and NASH) Excluded: anticoagulation, known VTE, palliative care
I	Patient divided into INR quartiles **[**<1.4, n=47**]** **[**1.4-1.6, n=61**]** **[**1.7-2.1, n=38**]** **[**>2.1, n=44**]**
E	Occurrence of VTE
S	Descriptive statistics Chi-squared/Fisher exact tests/Kruskal-Wallis/ANOVA

Chest. 2010; 137:1145-9.

Dabbagh et al. (2010)

Table 3—*Primary and Secondary Outcomes*

Characteristic	First Quartile INR < 1.4 (n = 47)	Second Quartile 1.4 ≤ INR < 1.7 (n = 61)	Third Quartile 1.7 ≤ INR < 2.2 (n = 38)	Fourth Quartile INR ≥ 2.2 (n = 44)	All (N = 190)	*P* Value
In-hospital VTE	3 (6)	3 (5)	4 (11)	2 (5)	12 (6.3)	.665
Hospital mortality	2 (4)	2 (3)	5 (13)	14 (32)	23 (12.1)	< .001
Hospital LOS, d (IQR)	3 (5)	4 (6)	4 (10)	5 (8)	4 (6)	.221
Diagnostic testing						
VD-US	10 (21.3)	19 (31.1)	12 (31.6)	19 (43.2)	60 (31.6)	.168
Spiral CT scan	10 (21.3)	16 (26.3)	11 (28.9)	9 (20.5)	46 (24.2)	.763
VQ scan	2 (4.3)	1 (1.6)	1 (2.6)	1 (2.3)	5 (2.6)	.864
DVT prophylaxis						
None	33 (70)	46 (75)	29 (76)	34 (77)	142 (74.7)	.603
Pharmacologic	7 (15)	5 (8)	1 (3)	4 (9)	17 (9)	.603
Mechanical	7 (15)	10 (16)	8 (21)	6 (14)	31 (16.3)	.603

Data are presented as No. (%) unless otherwise indicated. VD-US = venous Doppler ultrasound. VQ = ventilation-perfusion. See Table 1 for expansion of other abbreviations.

Chest. 2010; 137:1145-9.

Dabbagh et al. (2010)

- *"An elevated INR in the setting of CLD does not appear to protect against the development of hospital-acquired VTE."*

Chest. 2010; 137:1145-9.

Dabbagh et al. (2010)

Strengths	• Assessed “exposure-response” of INR elevation and VTE incidence • Baseline characteristics appear balanced • Appropriate outcome of symptomatic VTEs
Limitations	• Retrospective; documentation/code dependent • Small sample size / low number of events • VTE risk score (HF, transfusions, COPD, infections, etc) - 80% patients with cancer • No analysis of bleeding • No analysis of prophylaxis (data collected)

Edwards et al. (2011)

D	Retrospective chart review; 2008-2009
P	N=513 patients with INR >1.5 or PLT <100 x 10^6 admitted >72 hours to surgical ICU between Excluded: known VTE on admission, missing data for inclusion, heparin-induced thrombocytopenia
I	N=241, Chemical prophylaxis (included warfarin, IV UFH, etc) N=272, No chemical prophylaxis
E	Incidence of VTE (PE and DVT) - weekly duplex US (no bleeding outcomes)
S	Chi-squared/Fisher exact test

J Trauma. 2011;70: 1398–1400

Edwards et al. (2011)

TABLE 1. Patient Demographics and Outcomes

Variable	Overall (n = 517)	VTE Prophylaxis (n = 241)	No VTE Prophylaxis (n = 272)	*p*
Age, mean (SD)	625.6 (17.7)	65.8 (18.1)	65.4 (17.4)	0.8
Male sex	62.2%	61.4%	62.9%	0.78
Platelets, mean (SD)	105.9 (76.6)	115.7 (83.8)	97.2 (68.7)	0.01
Trauma patients	8.3%	8%	8.6%	0.87
Postoperative patients	82.6%	83.1%	82.1%	0.81
Cancer patients	26.1%	29.6%	22.9%	0.102
INR, mean (SD)	2.67 (2.69)	2.58 (2.10)	2.76 (3.12)	>0.95
APACHE, mean (SD)	24.4 (9.5)	23.9 (9.9)	24.8 (9.1)	0.31
Hospital LOS, mean (SD)	9.6 (10.3)	11.4 (9.6)	8.1 (10.7)	<0.0001
ICU mortality	19.5%	19.1%	19.9%	0.91
Hospital mortality	25.9%	28.2%	23.9%	0.27

J Trauma. 2011;70: 1398–1400

Edwards et al. (2011)

TABLE 2. Incidence of VTE and PE

Variable	Overall	VTE Prophylaxis	No VTE Prophylaxis	*p*
Incidence of VTE	84 (16.4%)	41 (17%)	43 (15.8%)	0.72
Incidence of PE	4 (0.8%)	3 (1.2%)	1 (0.4%)	0.35
		N=242	**N=271**	

J Trauma. 2011;70: 1398–1400

Edwards et al. (2011)

- *"Coagulopathic critically ill surgical patients remain at significant risk for VTE. Unfortunately, chemical VTE prophylaxis does not seem to decrease this risk."*

J Trauma. 2011;70: 1398–1400

Edwards et al. (2011)

Strengths	• Only known study to evaluate ICU patients • Assessed incidence of VTE with chemical prophylaxis vs. none
Limitations	• Retrospective • Bleeding??? • No attempt to adjust for bias/confounding • No adjustment for consistency/duration of chemical prophylaxis

Barclay et al. (2013)

D	Single-center, retrospective cohort study; 2008-2011
P	N=1581 cohort with chronic liver disease hospitalized (alcoholic, viral, cryptogenic, NASH) Excluded: active thrombosis, anticoagulation
I	Exposure: VTE prophylaxis (appropriate dose) Unexposed: No VTE prophylaxis
E	Primary outcomes: (1) occurrence of VTE or (2) bleeding during hospitalization
S	Multivariate conditional logistic regression

Pharmacotherapy 2013;33(4):375–382

Barclay et al. (2013)

Table 2. Outcome Measures

Outcome (No.)	No VTE Prophylaxis (n=1189)	VTE Prophylaxis (n=392)	p Value
Documented bleed	123 (10.3%)	8 (2.0%)	<0.001
VTE	21 (1.8%)	2 (0.5%)	0.050

VTE = venous thromboembolism.

Table 3. Risk Factors for Venous Thromboembolism in Patients With Chronic Liver Disease

	Odds Ratio	95% Confidence Interval
VTE prophylaxis	0.34	0.042–0.88
Active malignancy	8.76	2.56–29.58
Trauma or surgery during hospitalization	10.29	1.18–89.51
History of VTE	26.48	6.93–101.16

VTE = venous thromboembolism.

Pharmacotherapy 2013;33(4):375–382

Barclay et al. (2013)

- *"Pharmacologic VTE prophylaxis was associated with a decreased incidence of VTE in patients with CLD without an increased rate of bleeding and should be routinely considered on admission to the hospital."*

Pharmacotherapy 2013;33(4):375–382

Barclay et al. (2013)

Strengths	• Symptomatic VTE as outcome • Sufficient sample size • First to attempt at evaluating efficacy and safety of VTE prophylaxis in CLD • Reasonable attempts to control bias with multivariate regression
Limitations	• Retrospective • Relies on ICD-9 coding and chart documentation • Differences in baseline characteristics may account for differences in rates of bleed/VTE

Summary

Study	Population	INR impact on VTE	Impact of pharmacologic prophylaxis on VTE risk
Northup et al. 2006	Cirrhosis	⟷	Not studied
Gulley et al. 2008	+/- cirrhosis +/- chronic diseases	⟷	Not studied
Dabbagh et al. 2010	All CLD in INR quartiles	⟷	Not studied

Summary

Study	Population	INR impact on VTE	Impact of pharmacologic prophylaxis
Edwards et al. 2011	Medical/Surgical ICU with mean INR 2.67	Not studied	↔ VTE ? bleeding
Barclay et al. 2013	CLD with mean INR ~1.4	↔	↓ VTE ↓ bleeding

Conclusions

- Efficacy and safety of pharmacologic or mechanical prophylaxis for VTE is not well characterized
- Risk in non-cirrhotic patients are likely the same in cirrhotic patients
- Acute liver injury and risk of thrombosis/bleeding is unknown

Conclusions

Is the INR a useful parameter for assessing the benefit of VTE prophylaxis in hospitalized adult patients with liver disease?

NO.

Questions.