Patient Blood Management in Liver Surgery

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Conflicts of Interest

- CSL Behring GmbH
- Werfen
- MSD
- AstraZeneca
- Gilead
- Biotest

Reason for liver resection

Malignant tumor	Benign Tumor
Primary liver tumor (HCC in cirrhosis) **Colorectal metastasis** **Cholangiocellular Carcinoma**	**Hepatic Adenoma** **Hämangioma**

Latchana, Langenbecks Archives of Surgery , 2019, 404: 1-9

Blood loss and transfusion in hepatectomy

- Transfusion rate 25.2%-56.8%
- Reason for differences
  - Different patient population
  - Different time line
- Data base provides inside into nature of the problem

Bennett, HBP, 2017 19(4): 321-330
Marwah, HBP, 2007 9 (1) 29-39
Hallet, Hepatobiliary Surg Nutr 2018 7 (1): 1-10

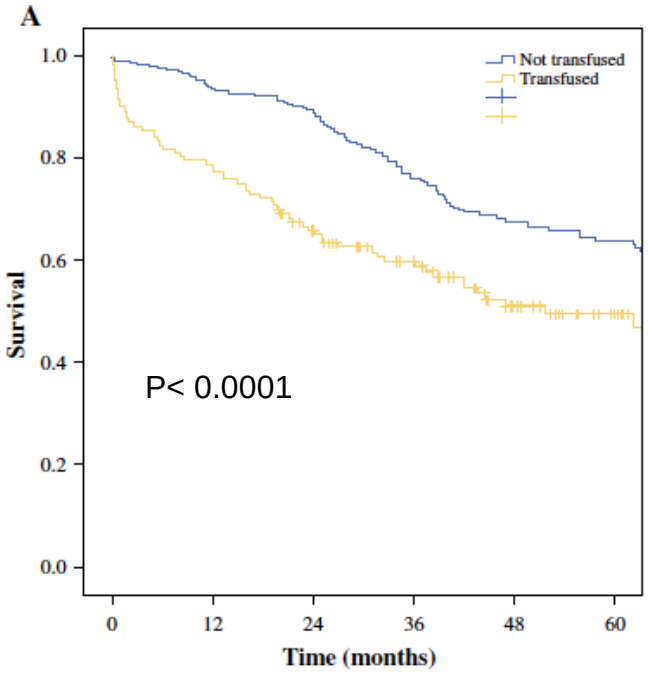
Short term outcome and higher rate of Transfusion

- Higher surgical morbidity with increased transfusion rate
  - 28.3% vs. 11.1 % ($p < 0.0001$)
- Higher 30-day Mortality
  - 5.6% vs. 1%
- Multivariate Analysis and risk adjustment
  - RBC transfusion independet risk factor for morbidity (RR = 1.8) and 30-day Mortality (RR = 3.62)
- Immunmodulatory effects
  - Higher susceptibility to infection/Sepsis

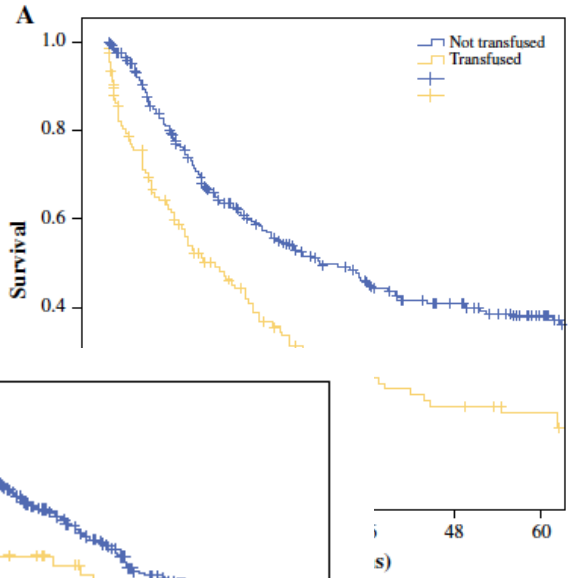
Vamvakas, Blood Rev 2007 21 (6): 327-348
Hallet, HepatoBiliary Surg Nutr. 2018, 7 (1); 1-10

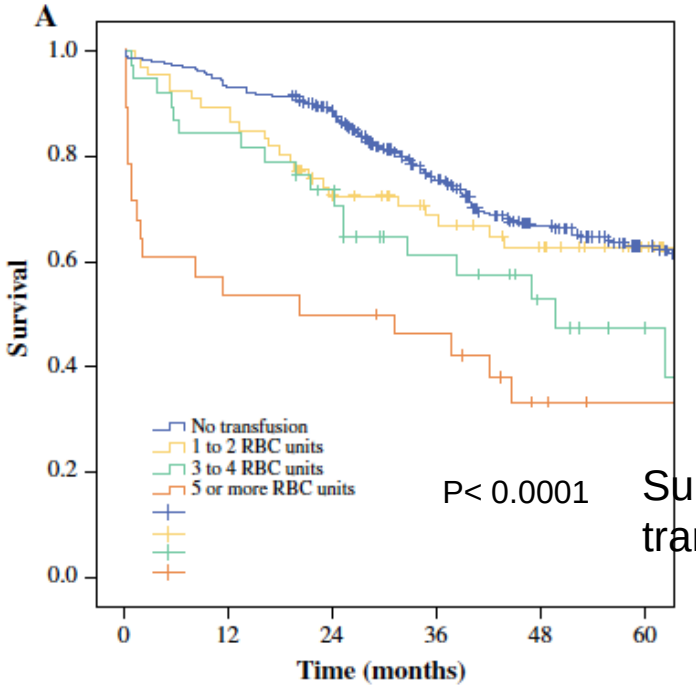
Oncologic outcomes

Overall survival



Recurrence free survival





Survival in dependence of transfused RBCs

Hallet, Ann Surg Oncol, 2015, DOI10.1245/s10434-015-4477-4

Many reasons to avoid transfusion

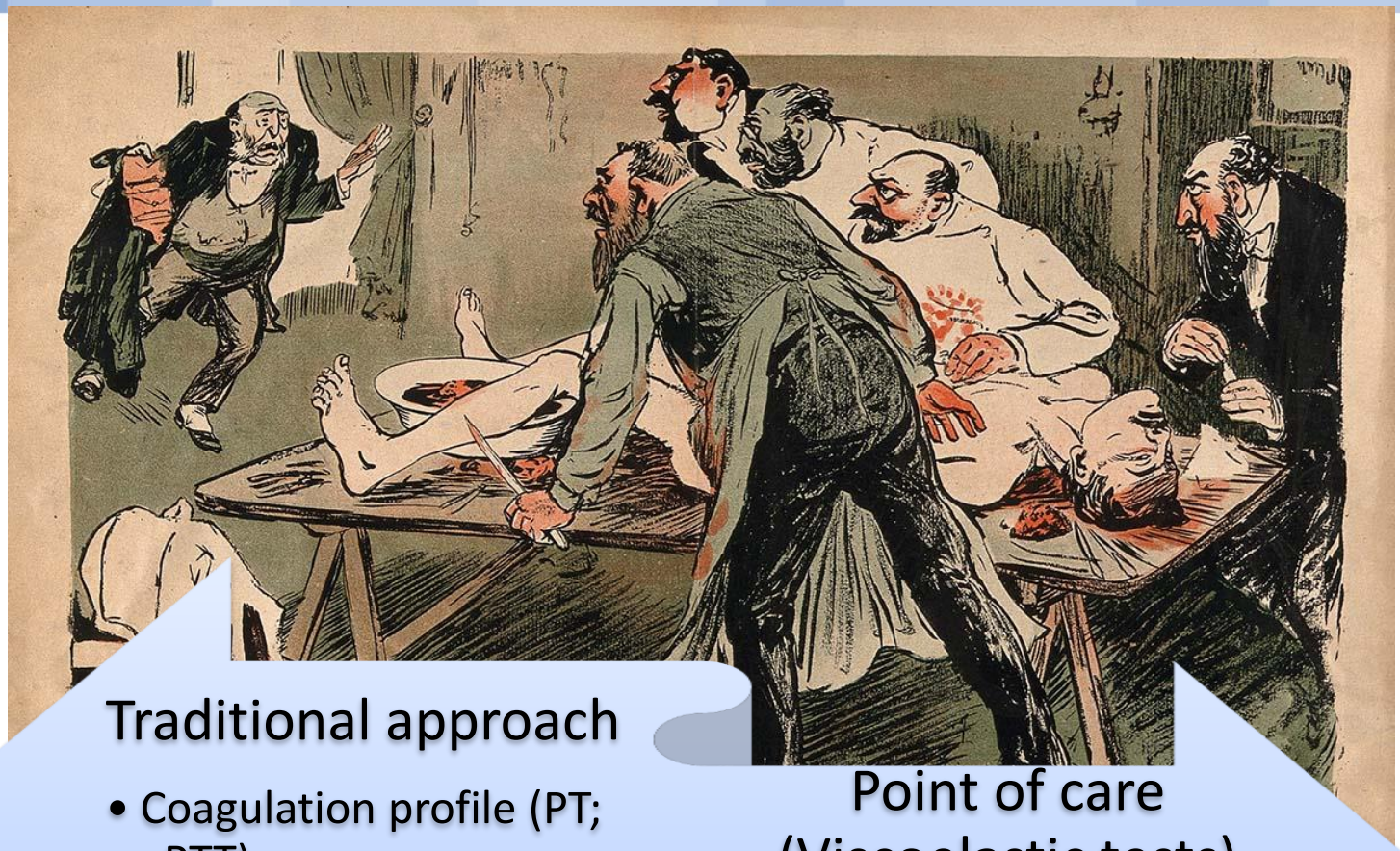
Patient blood management in Liver surgery

Pre-Op	Intra-Op	Post-Op
Assessment of bleeding risk Anemia Cirrhosis Extent of resection	Pringle maneuver Low CVP policy Fluid restriction Tranexamic acid	Low transfusion trigger Reduce number of blood parameter assessment Low volume blood samples

Preop. Assessment of Bleeding Risk

- Medical coagulation history patient
- Extent and location of resection => risk of bleeding
- Resection in cirrhosis?
- Laboratory

Assessment of bleeding risk



Traditional approach

- Coagulation profile (PT; aPTT)
- Platelet count

Point of care (Viscoelastic tests)

Rotem

TEG

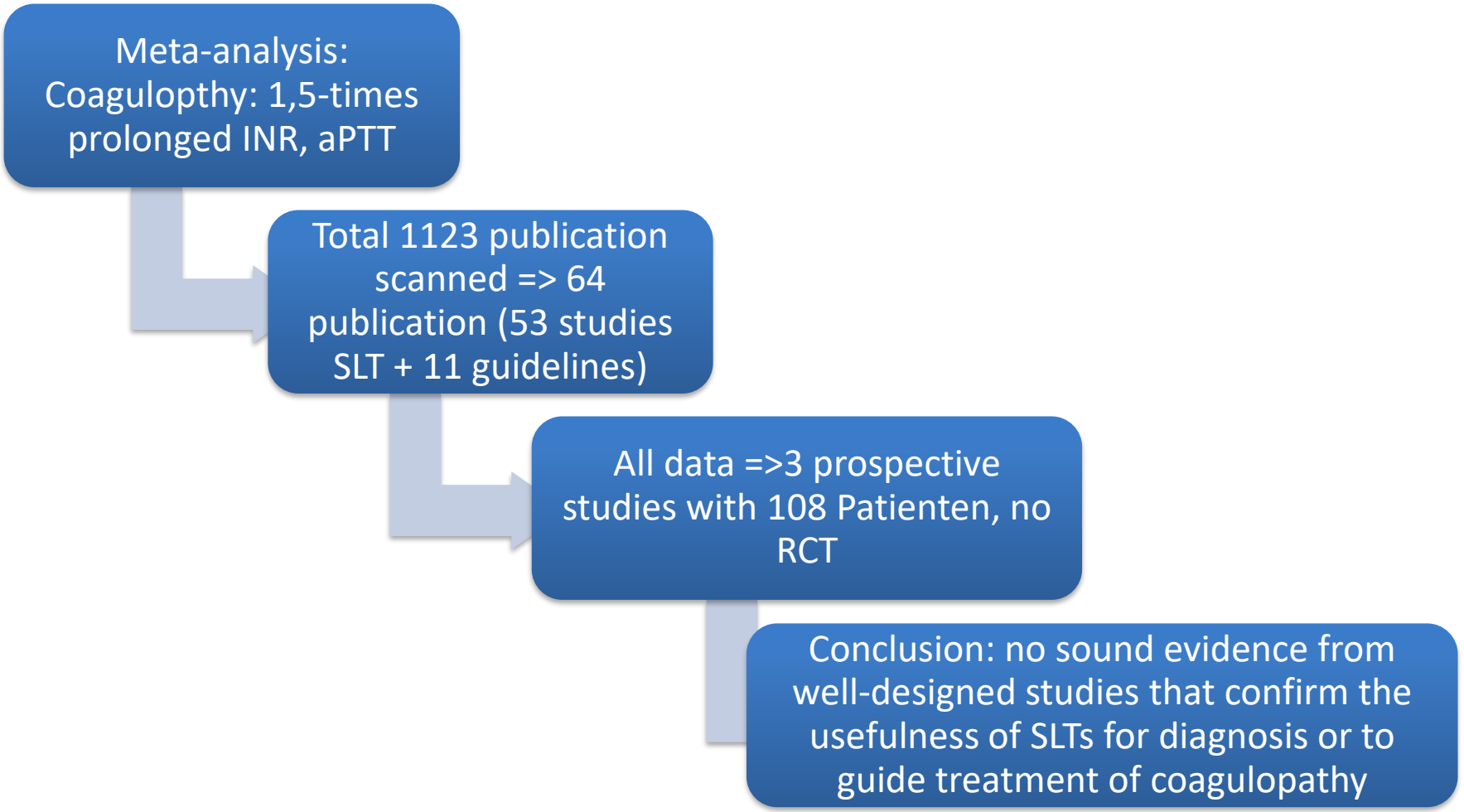
Paucity of studies to support that abnormal coagulation test results predict bleeding in the setting of invasive procedure. An evidence-based review

- One trial and 24 oberservational studies

CONCLUSION: There is insufficient evidence to conclude that abnormal test results predict bleeding. Randomized controlled trials should be performed to provide stronger evidence for clinical decision making regarding preprocedure transfusion.

Segal, Transfusion 2005; 45: 1413-1425

Standard laboratory test (SLT) and assessment of bleeding risk



Haas, British J Anaesthesia 114 (2): 217-224, 2015

TEG guided coagulation management before invasive procedure

N = 60 Patienten
1:1 Allocation TEG vs. SLT

r > prolonged => FFPs

MA < 30 mm => PV

INR = 1.8

PLT: 50/nl

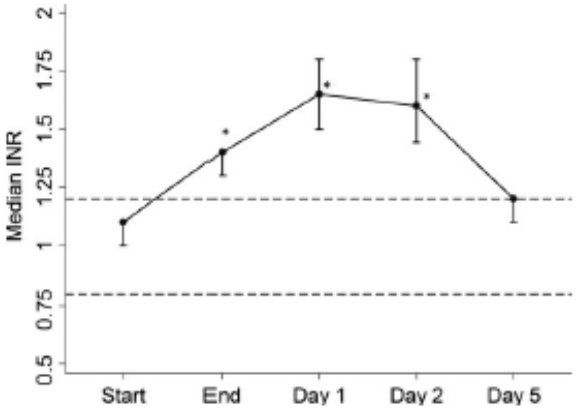
Pietri, Hepatology 2015, doi: 10.1002/hep.28148T

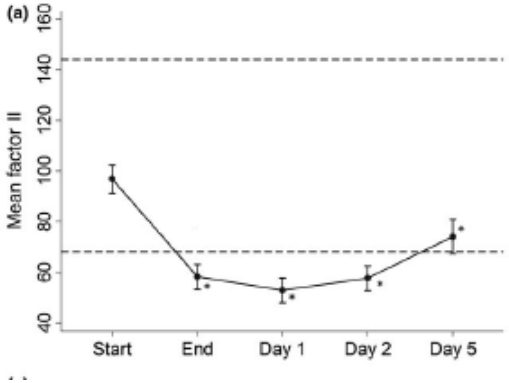
TEG guided coagulation management before invasive procedure

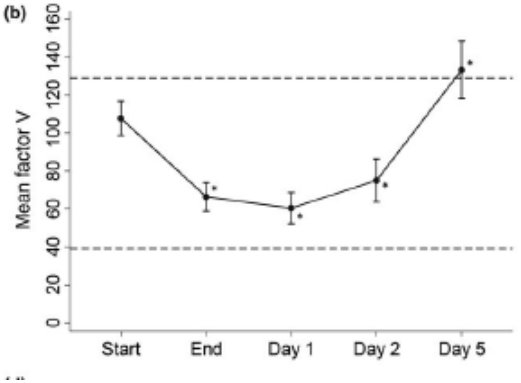
	SLT	TEG	p-value
Transfusion rate	100%	16,7%	<0.0001
FFP	53.3%	0% alone	0.0001
Platelet	33.3%	6.7%	0.009
FFP+platelet	13.3%	10%	n.s.
Post-Procedure HB	9,9 ± 1.2	10.7 ± 1.8	0.043
Postprocedure related bleeding	1 (3.3%)	0	0.313
Postprocedure INR	1.75 ± 0.41	1.9 ± 0.64	0.225
Postprocedure Platelet count	58.3 ± 31.3	55.2 ± 27.5	0.692

Pietri, Hepatology 2015, doi: 10.1002/hep.28148T

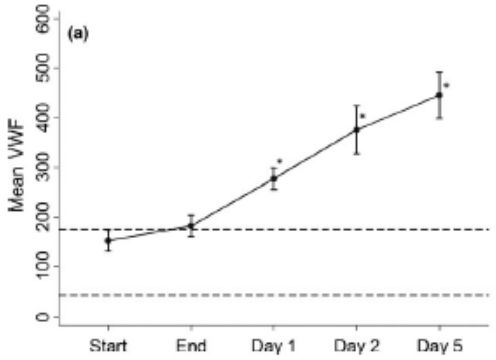
Alterations in coagulation following major liver resection

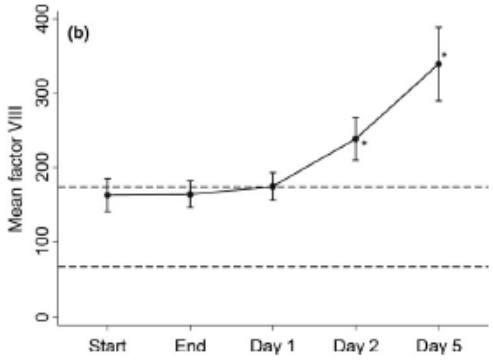






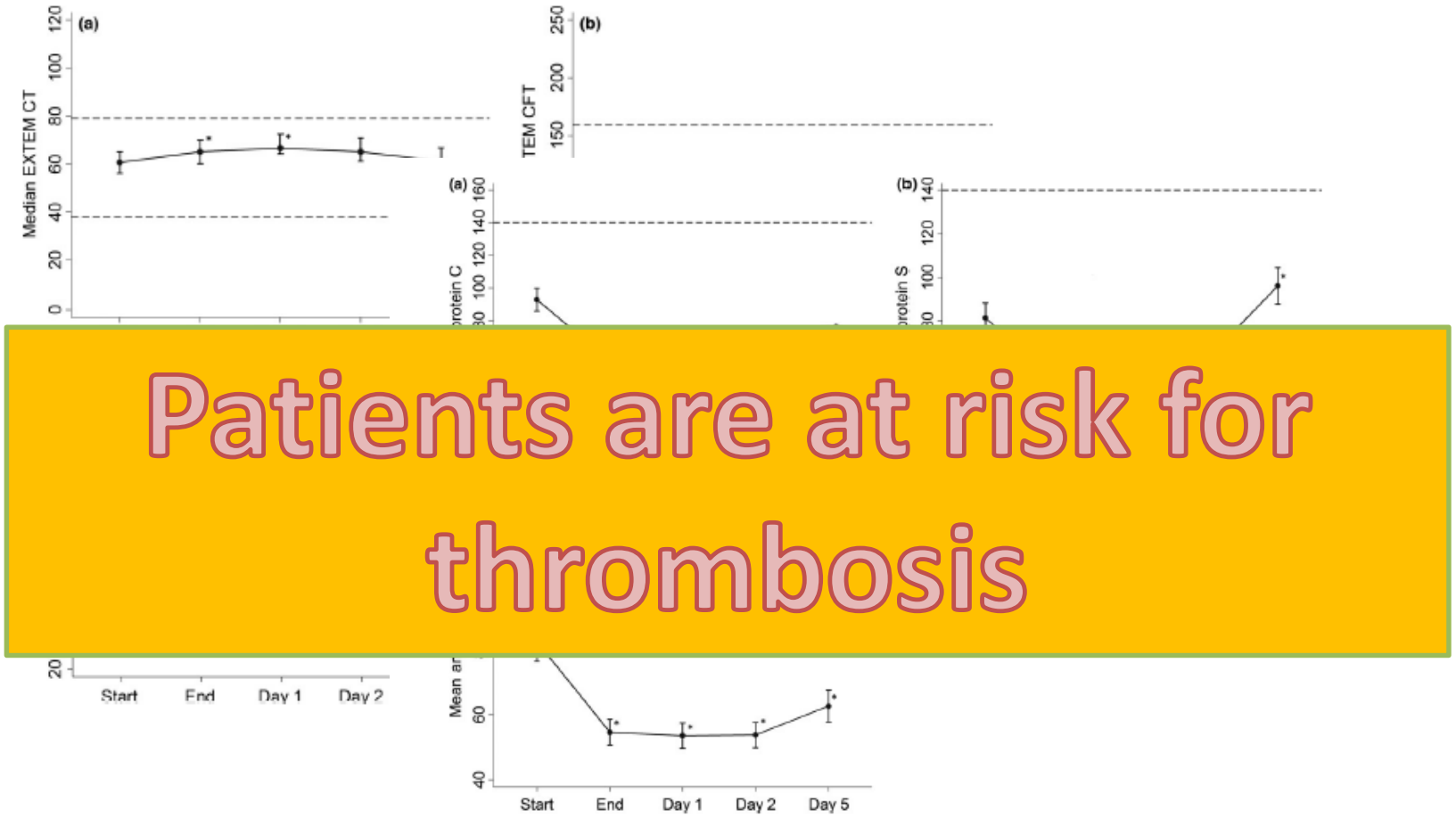
CI. Dashed lines are reference ranges. *p < 0.01 compared with baseline.





Mallett, Anaesthesia 2016, 71 657-668

Alterations in coagulation following major lliver resection



Patients are at risk for thrombosis

Mallett, Anaesthesia 2016, 71 657-668

Liver Failure and Risk of Thrombosis

- Registry data from Denmark 1980-2005
- N= 496 872, whereas 99 444 pulmonary embolism

Table 4. **Relative risks[a] (odds ratios) and 95% CIs for VTE**

Variable	All venous thromboembolism		Unprovoked venous thromboembolism	
	Crude RR	Adjusted[b] RR	Crude RR	Adjusted[c] RR
Liver cirrhosis	2.60 (2.34–2.88)	1.74 (1.54–1.95)	2.88 (2.52–3.29)	2.06 (1.79–2.38)
Non-cirrhotic liver disease	2.54 (2.36–2.73)	1.87 (1.73–2.03)	2.84 (2.59–3.11)	2.10 (1.91–2.31)
Liver cirrhosis and HCC	2.64 (2.38–2.93)	1.75 (1.56–1.97)	2.90 (2.54–3.32)	2.08 (1.81–2.40)

HCC, hepatocellular carcinoma.

[a]Computed with conditional logistic regression. [b]Adjusted for cancer, fractures, trauma, surgery, pregnancy, Charlson Index, psychiatric diseases, and obesity. [c]Adjusted for Charlson Index, psychiatric diseases, and obesity.

Søgaard, Am J Gastro 2009, 104, 96-101

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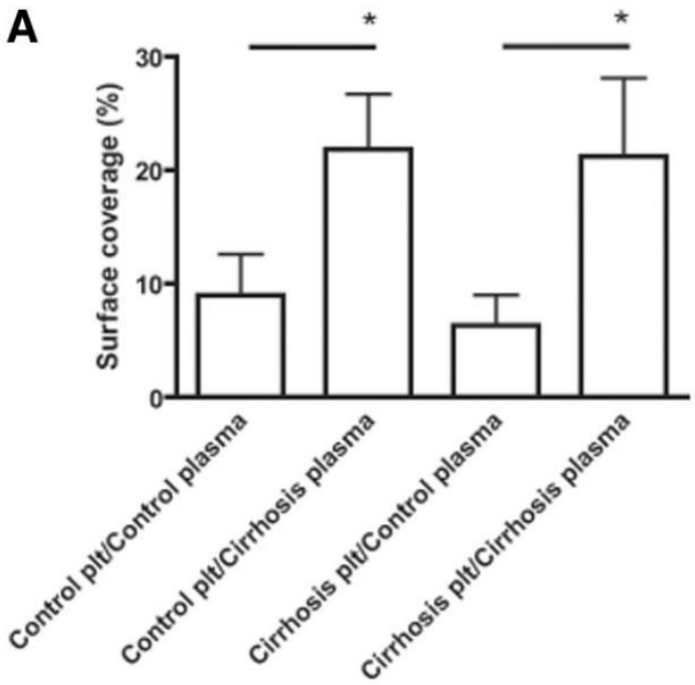
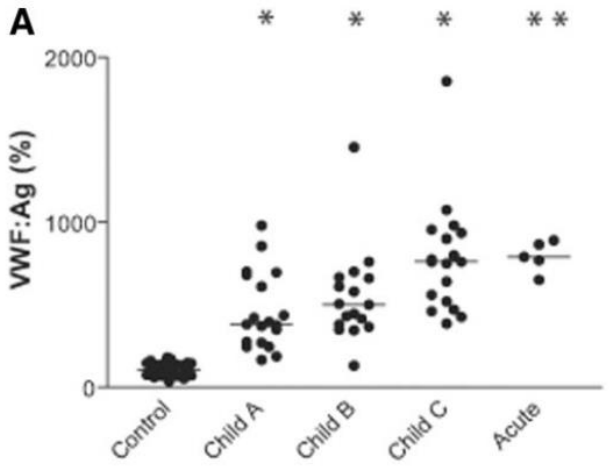
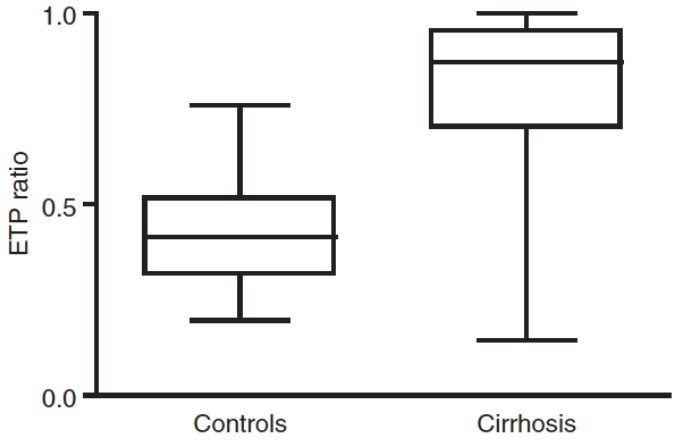
Increased platelet adhesion and aggregation due increased vWF

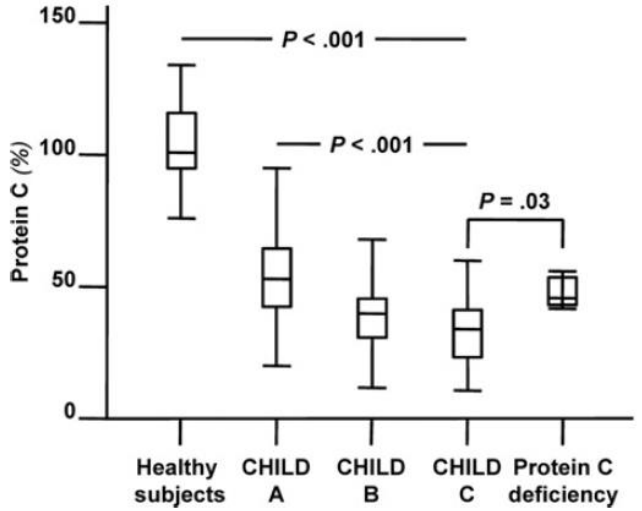




Lisman, Hepatology 2006, 44:53-61

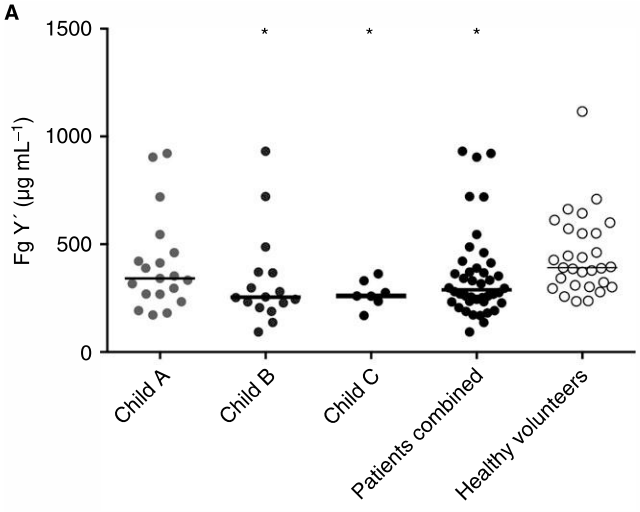
Endothel Thrombin generation increased und Protein C serum level decreased

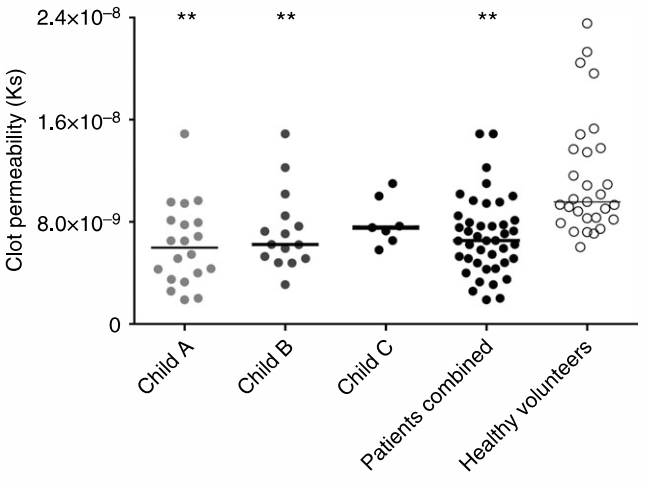




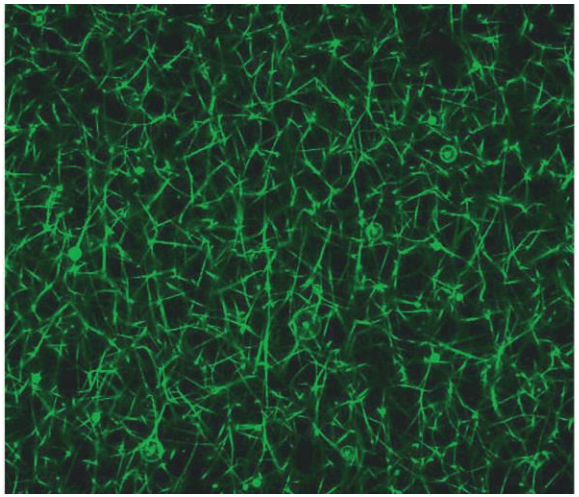
Gatt, Journal of Thrombosis and Hemostasis, 2010, 8: 1994-2000
Tripodi, Gastroenterology 2009: 137: 2105-2111

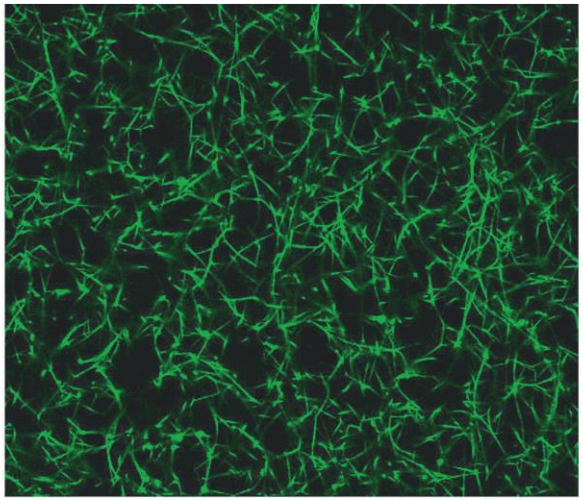
Procoagulant changes in fibrin clot structure in patients with cirrhosis are associated with oxidative modifications of fibrinogen





CHILD B cirrhosis





Healthy volunteer

Hugenholtz, JTH, 2016; 14: 1054-1066

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North Pacific Surgical Association: The INR overestimates coagulopathy in patients after major hepatectomy

Abstract

BACKGROUND: The International Normalized Ratio (INR) is commonly used to guide therapy after hepatectomy. We hypothesized that the use of thrombelastography (TEG) would demonstrate a decreased incidence of hypocoagulability in this patient population.

METHODS: Seventy-eight patients were prospectively enrolled before undergoing hepatectomy. INR, TEG, and coagulation factors were drawn before incision, postoperatively, and on postoperative days 1, 3, and 5.

RESULTS: Patients demonstrated an elevated INR at all postoperative time points. However, TEG demonstrated a decreased R value postoperatively, with subsequent normalization. Other TEG measurements were equivalent to preoperative values. All procoagulant factors save factor VIII decreased postoperatively, with a simultaneous decrease in protein C.

CONCLUSIONS: TEG demonstrated a brief hypercoagulable state after major hepatectomy, with coagulation subsequently normalizing. The INR significantly overestimates hypocoagulability after hepatectomy and these data call into question current practices using the INR to guide therapy in this patient population.

Louis, Am J Surg 2014; 207, 723-727

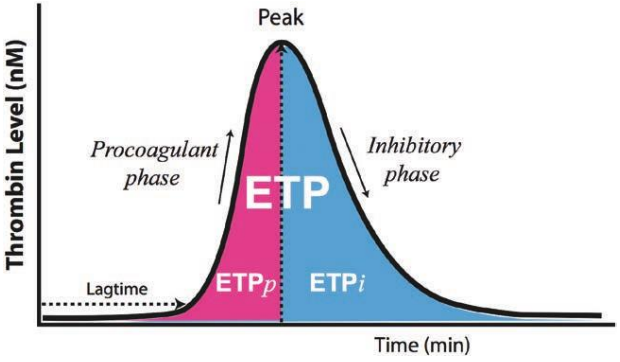
Liver surgery and thrombosis

- N = 27 Pat. With Cholangio-cellular cancer vs. Living donor Right hepatectomy

Table 3 Thromboelastometry data (initiation, propagation, firmness, and lysis) of control and cholangiocarcinoma group

	Control ($n=17$)	Cholangiocarcinoma ($n=27$)	Unadjusted P value	Bonferroni-adjusted P value	Normal range
CT (s)	67 (58–74)	61 (52–68)	0.072	0.576	40–80
CFT (s)	106 (85–123)	56 (48–79)	0.000	0.001	50–150
v-Max (mm/s)	12 (11–15)	22 (19–28)	0.000	0.000	–
t-Max (s)	126 (99–145)	86 (76–104)	0.007	0.055	–
AUC	6412 (6049–6632)	7354 (6687–7684)	0.000	0.000	–
MCF (mm)	64 (61–66)	74 (67–77)	0.000	0.000	50–70
G (dynes/cm^2)	8759 (7713–9841)	13622 (9143–16742)	0.000	0.006	$5–12 \times 10^9$
ML%	10 (9–13)	4 (9–13)	0.131	1.000	<15%

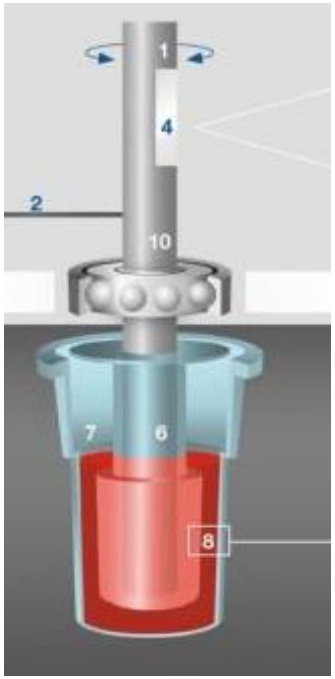
Data are shown as median (IQR). AUC, area under the curve; CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness; ML, maximum lysis; t-Max, time to reach the maximum velocity; v-Max, maximum velocity.



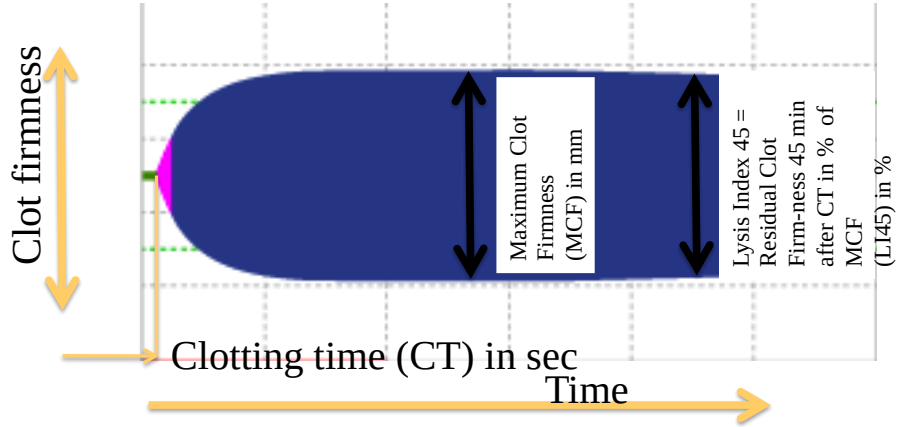
- 6 Thrombotic events only in the Cancer group
  - 4 portal vein thrombosis
  - 2 deep vein thrombosis

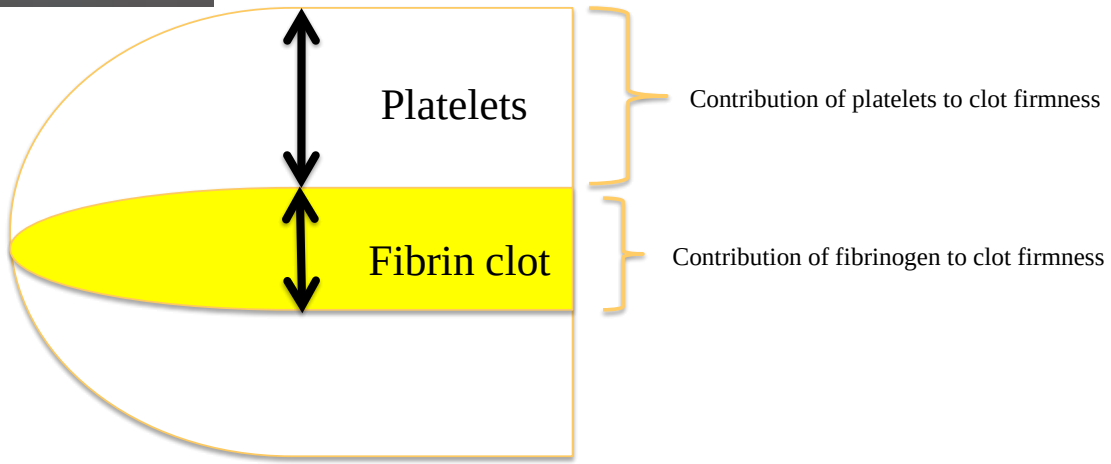
Blasi, Blood, Coagulation, Fibrinolysis 2018, 29, 61-66

Diagnoses and treatment guided with Visco-elastic tests



Thrombelastometry Function variables





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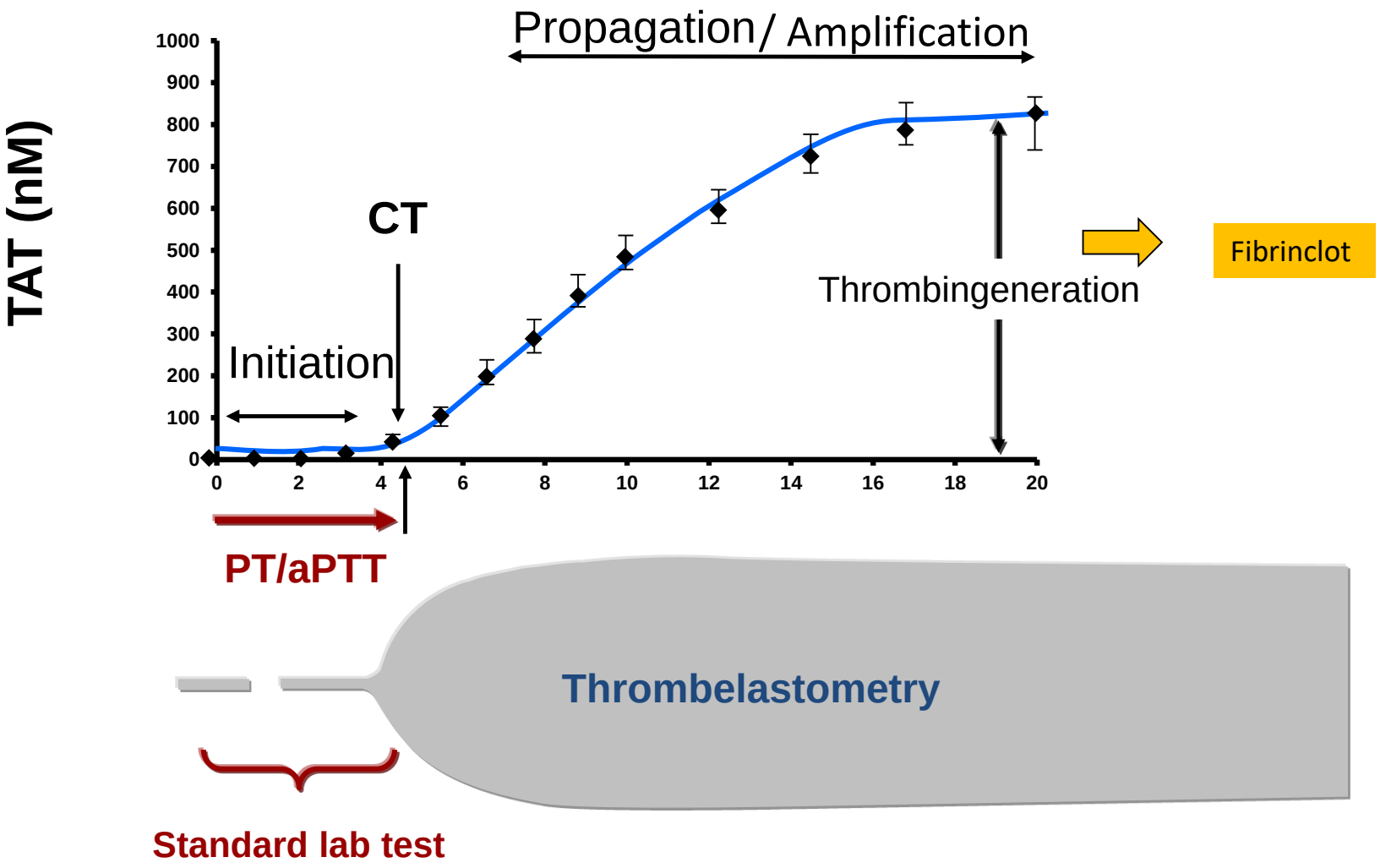
Thrombin Generation



Turn around time SLT vs. Rotem

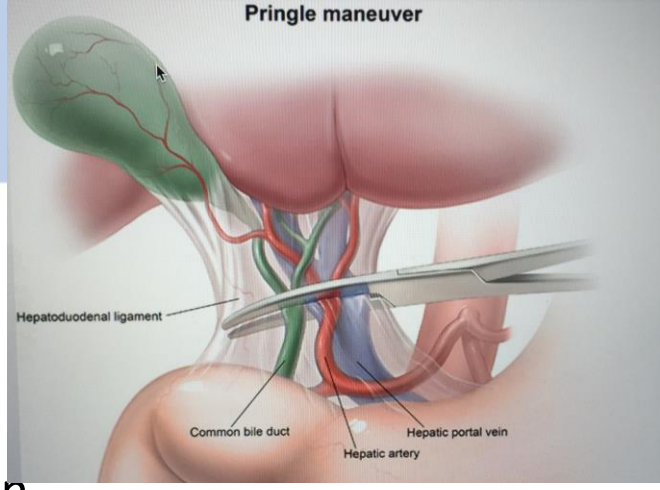
- For better comparison both devices in Lab
- SLT: 53 min vs 23 min. POC , p< 0.001
- If POC is bedside: turn around time < 10 min (A5)

Haas, BJA 2012, 108, 36-41

Intraoperative Strategies to avoid bleeding

- Pringle maneuver (portal pedicle clamping)
- CVP ≤ 5 mmHg
- Fluid restriction
- Hemostatic agents (oxidized ceullulose, fibrin, collagen)
- Antifibrinolytics

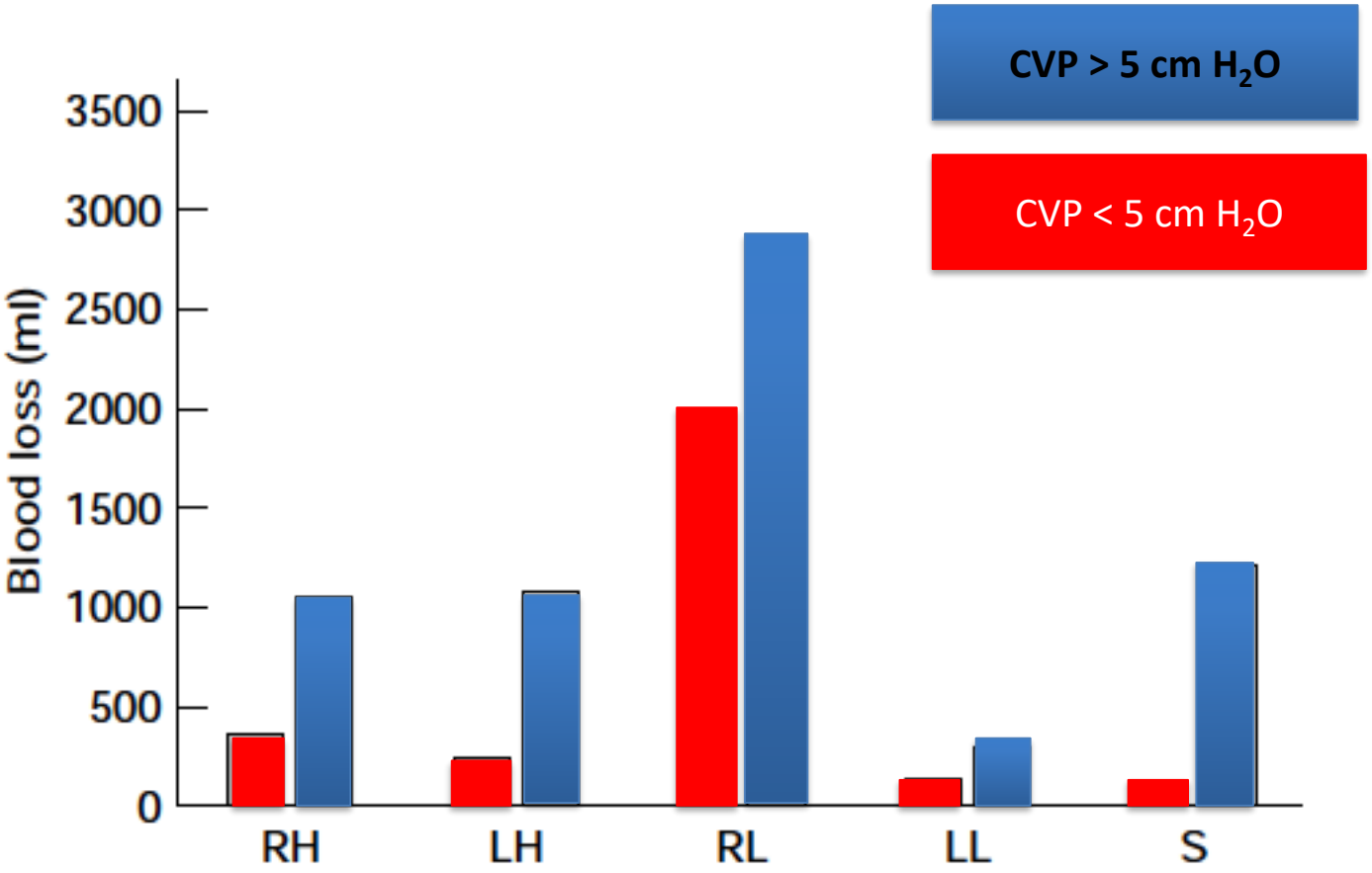
Pringle Maneuver



- First described in 1908
  - Clamping 10-20 min, with 5 min gap for reperfusion
  - It was shown to be safe up to 120 min
- Concern:
  - Postop liver (ischemic hepatitis)
  - Earlier recurrence of malignant tumor (Ischemia/Reperfusion)
- Cochrane Database systematic Review
  - Well tolerated
  - Reduce blood loss
  - No Difference in term of Morbidity and Mortality

Pringle, Ann Surg 1908, 48: 541-549
Gurusamy, Cochrane Database of Systematic Review 2009, DOI 10.11002

CVP and liver surgery



R M Jones et al British Journal of Surgery 1998, **85**, 1058–1060

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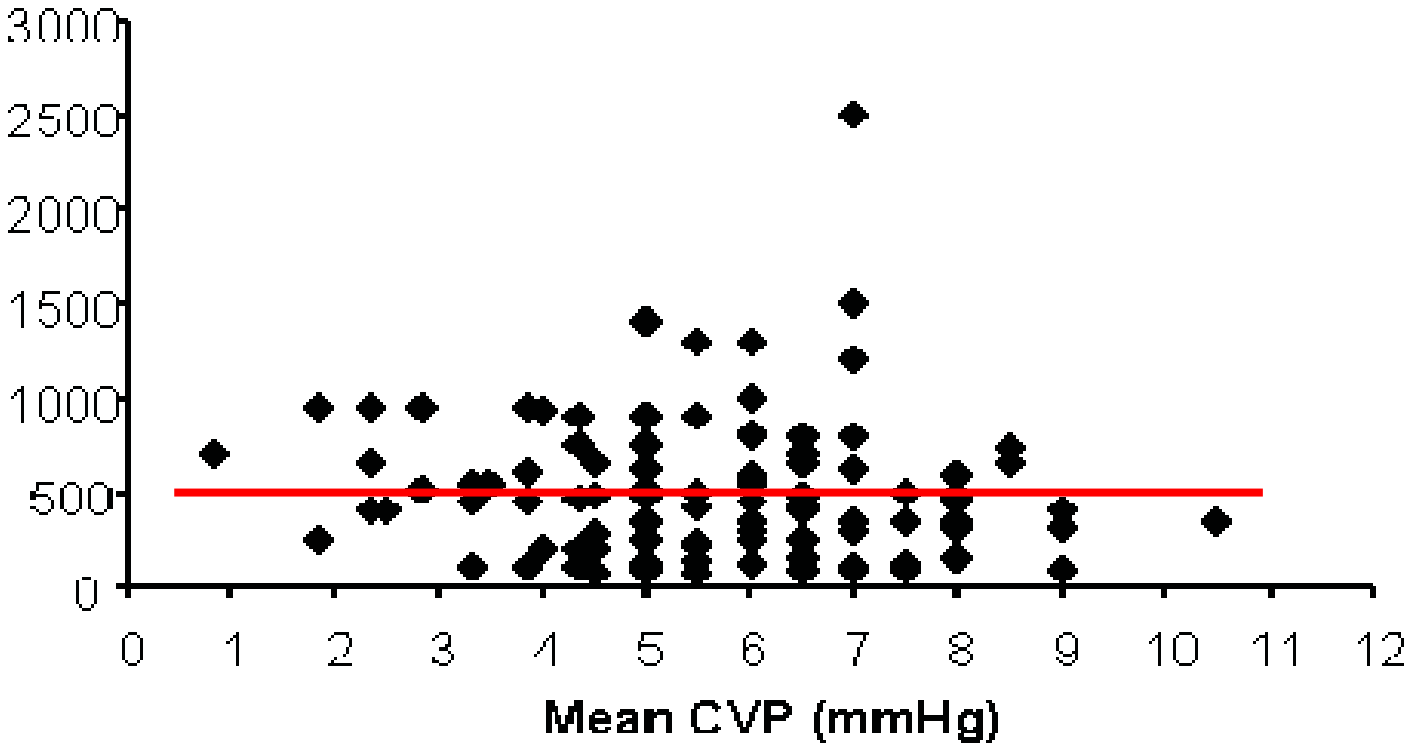
Anesthesia Care for Adult Live Donor Hepatectomy: Our Experiences With 100 Cases



Chhibbar, Liver Transplantation, 2007, 13:537-542

Low CVP in ESLD

- Among 500 LTX 79.6% without blood products (Transfusion 2012; 93: 1276-1281)
- Impact of Phlebotomy and phenylephrine on PVP and CVP before and after Intervention

Massicotte, Transplantation 2010; 89: 920-927

PVP = portal venous pressure
CVP = central venous pressure

Effect on CVP

Central venous pressure			
Before phlebotomy (mm Hg)	After phlebotomy (mm Hg)	Delta 1	After phenylephrine (mm Hg)
14	8	0.4	11
12	6	0.5	8
10	4	0.6	9
12	7	0.4	10
13	8	0.4	11
13	8	0.4	14
18	7	0.6	13
21	15	0.3	17
9	5	0.4	8
15	7	0.5	12
Median 13	07		11

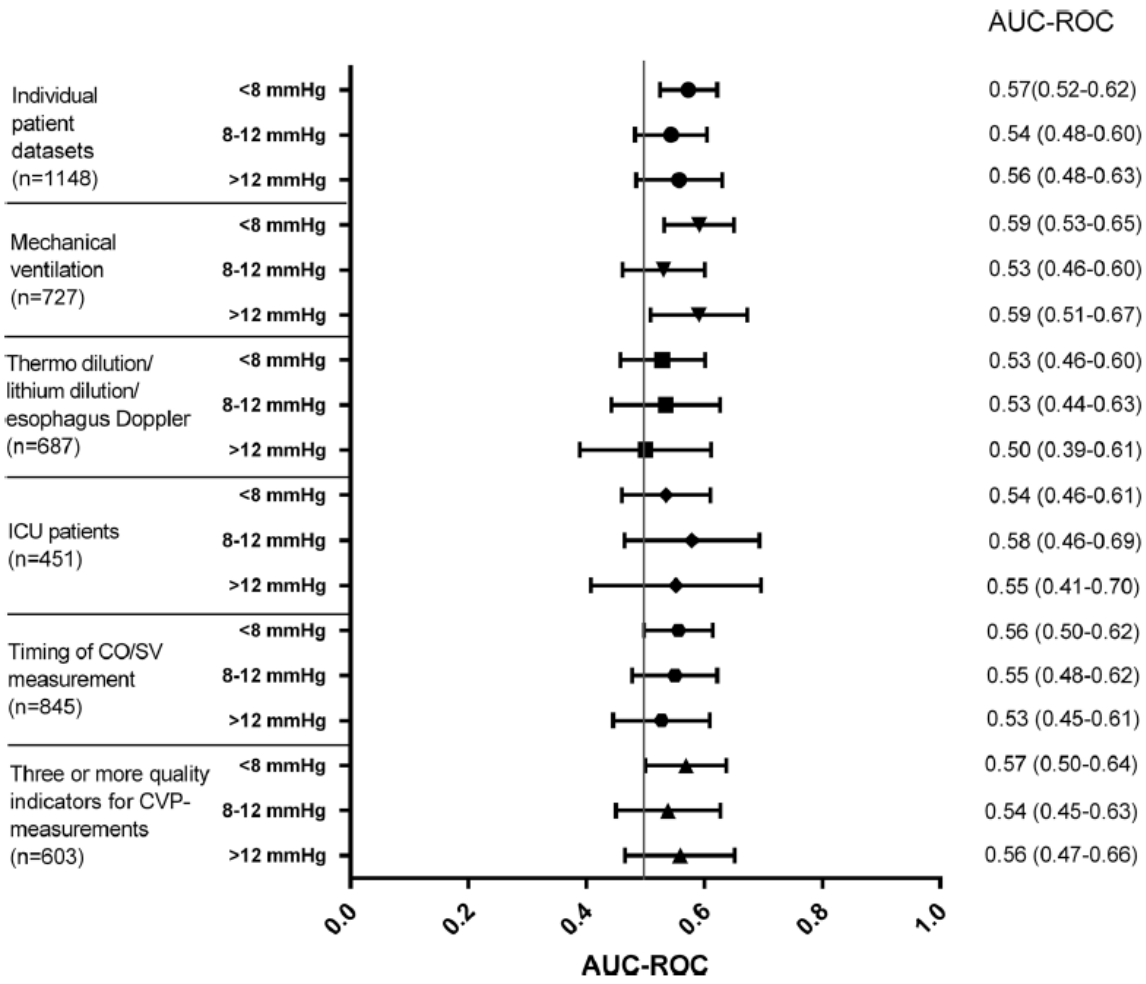
Massicotte, Transplantation 2010; 89: 920-927

Effect on PVP

Portal venous pressure				
Before phlebotomy (mm Hg)	After phlebotomy (mm Hg)	Delta 1	After phenylephrine (mm Hg)	Delta 2
32	19	0.4	18	0.1
24	12	0.5	13	−0.1
32	15	0.5	15	0
13	7	0.5	8	−0.1
29	19	0.3	15	0.2
12	8	0.3	7	0.1
9	4	0.6	5	−0.3
14	10	0.3	10	0
8	3	0.6	3	0
10	4	0.6	3	0.3
Median 18	→ 09		→ 09	

Massicotte, Transplantation 2010; 89: 920-927

Systematic Review on 1148 Patients- Evaluation CVP for volume replacement (total 51 studies)



Esekesen, Int. Care Med. 2016, 42: 324-332

Central venous pressure and liver resection: a systematic review and meta-analysis

Abstract

Background: A liver resection under low central venous pressure (CVP) has become standard practice; however, the benefits beyond a reduction in blood loss are not well reported. Moreover, the precise method to achieve CVP reduction has not been established. A systematic review and meta-analysis of randomized controlled trials (RTCs) was performed to assess the effects of CVP on clinical outcome and to identify the optimum method of CVP reduction.

reduction were associated with a reduced post-operative morbidity.

Conclusion: Low CVP surgery is associated with a reduction in EBL; however, this does not translate into an improvement in post-operative morbidity. The optimum method of CVP reduction has not been identified.

Reduction ranges from 308-406 ml blood

Hughes, HPB, 2015, 17, 863-871

Fluid restriction in liver surgery is benefical

Healthy volunteer
Volume load

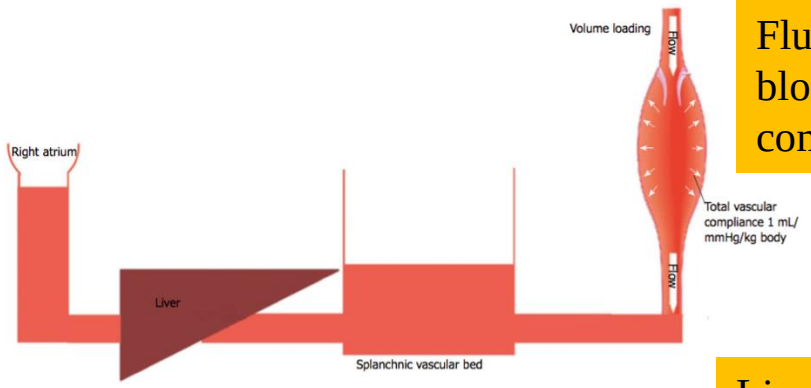
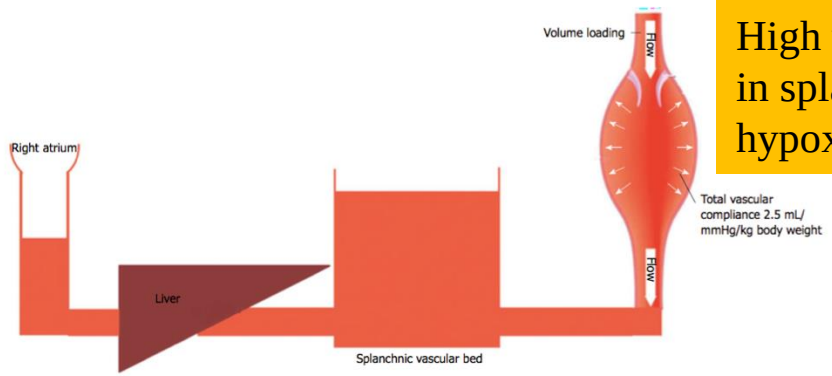


Figure 1 Fluid loading in a healthy subject. Low vascular compliance combined with decreased pooling of blood in splanchnic circula increased central venous pressure.

Volunteer:
Fluid load increase MAP and central blood volume due to low vascular compliance



Liver resection:
Volume load less MAP increase;
High vascular compliance, blood pooling in splanchnicus bed. Edema, tissue hypoxia

Patient during Liver resection and transient portal hypertension

Mukhtar, WJG 2016, DOI: 10.3748/wjg.v22.i4.1

Use of antifibrinolytics

- Hyperfibrinolysis is shown in Trauma, liver transplantation, cardiac surgery
- In liver resection unknown
- Blind Use of antifibrinolytics was common in the frist decade 2000 to avoid blood loss

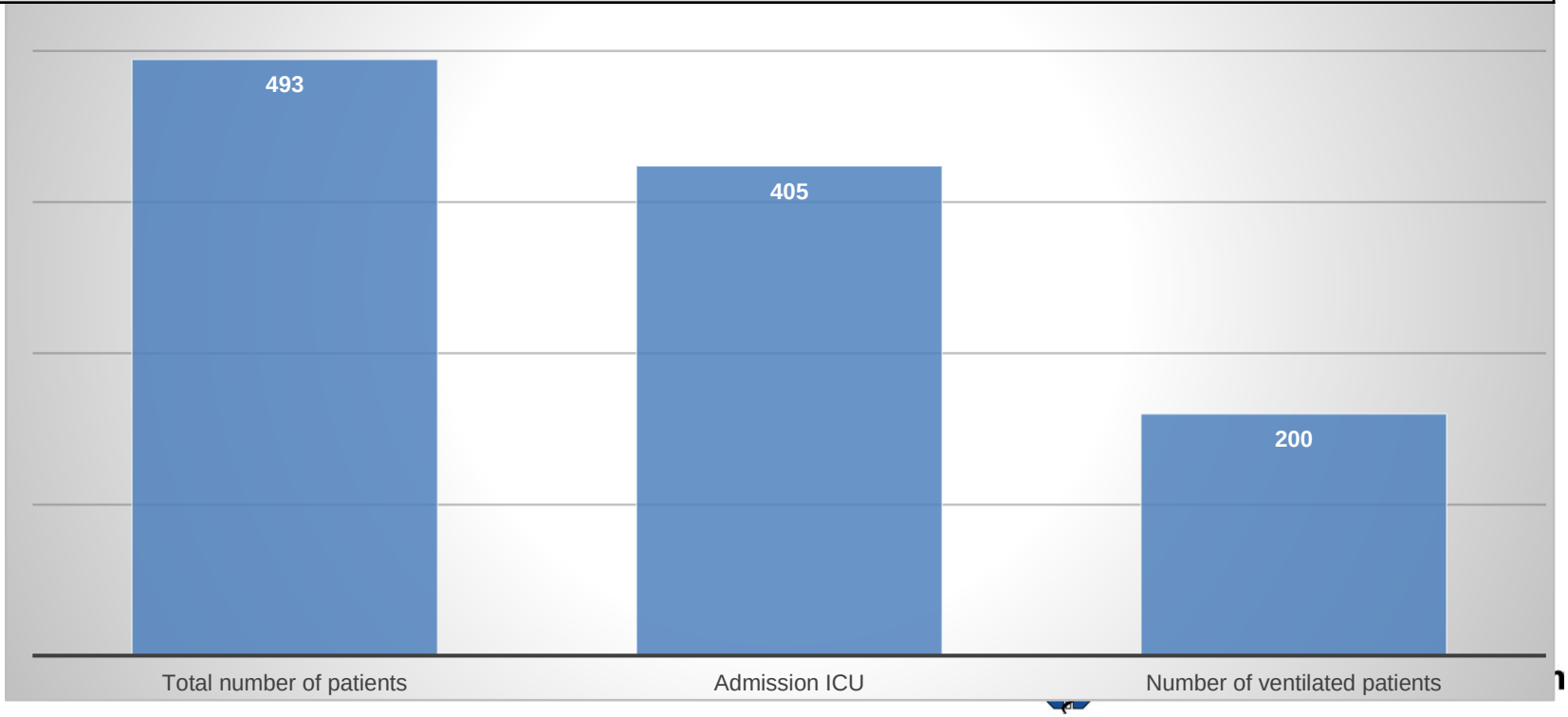
Use of antifibrinolytics in liver surgery

Author	Journal	Drug	Year	Operation	Number of patients	Transfusion requirement	Thromb-osis
Porte (RCT)	Lancet	Aprotinin	2000	LT	46/43/48	Decreased 37%	no
Wu							
Mol (Syst revie Met Anal							ed
Kara olas		dose)			lysis)		ed

Studies very old
Change of management
No robust data

Liver resection Medical Center University Duisburg-Essen in 1/2015 - 10/2016 (≥ 2 segment resection)

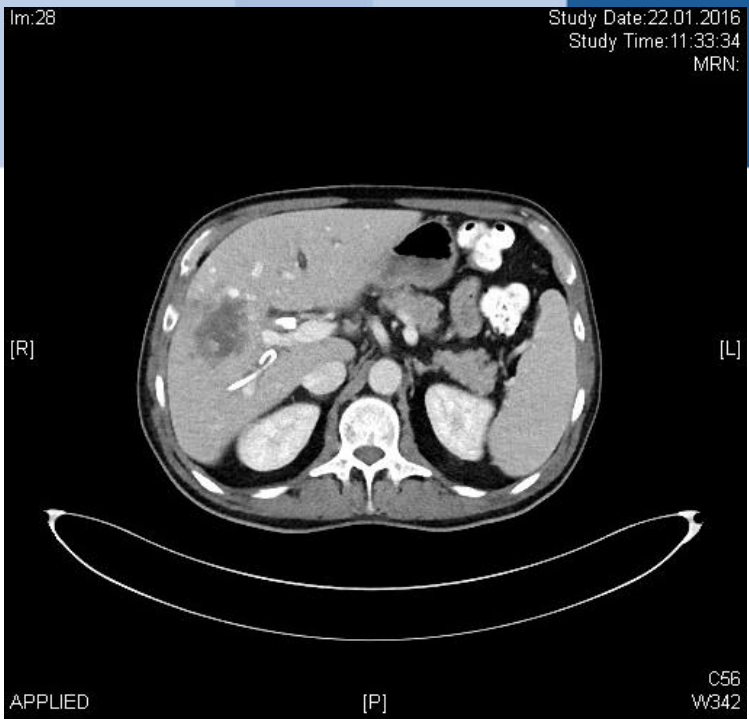
ICU stay (days)	1.8 (0.9-4.1)
Ventilation time (h)	12.25 (5.3-52.58)
Hospital stay (days)	11.2 (14-136.1)
Transfusion rate	7.5% (37/493 Patients)
Transfused RBC in transfused Pat.	4 (1-5.5)
In-house mortality (%)	6.6



Policy Essen liver surgery

- Low transfusion trigger (7 g/dl and sometimes less)
- Coagulation management => VET-guided coagulation concentrate replacement, no FFP
- Fluid restriction
- CVP appreciates not so much attention (Surgeons quit to ask CVP numbers)

Case report-60 ys. Old patient

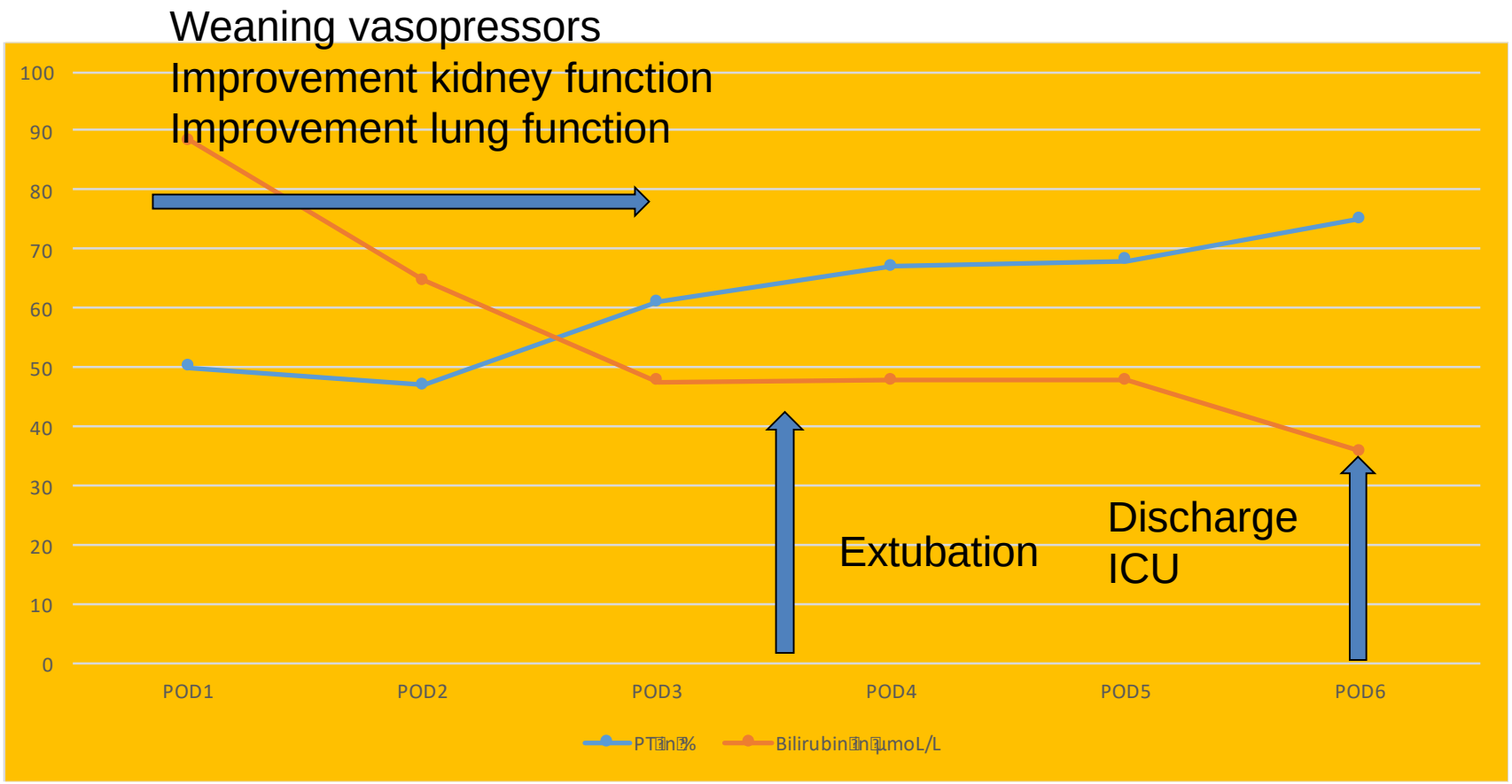


- 60 ys old male patient
- Klatskin tumor type Bismuth IIIa
- IDDM
- Smoker
- Operation:
- Extended right hepatectomy (right hepatectomy + Seg IV)
- Resection bile duct and Hepatico-Jejunostomy
- Infiltration of Portal vein => PV resection and reconstruction
- Duration: 5 hours, 5000 ml Cristalloids, 1000 ml Colloids, 2 RBC

ICU admission and the first 24 h

Liver	bilirubin: 5.2 mg/dl= 88.9 µmol/L (12 h after ICU admission)
Kidney	10ml/h (< 0.5 ml/kg/h) within first 24 h
Hemodynamic	Norepinephrine 1.2 µg/kg/min
Ventilation	BIPAP, P_{insp} = 25 mbar, PEEP = 10 mbar, FiO_2 = 60% Horovitz-Index: 175 mmHg

ICU Course-lab course PT and bilirubin



Grade C postop Liver Failure

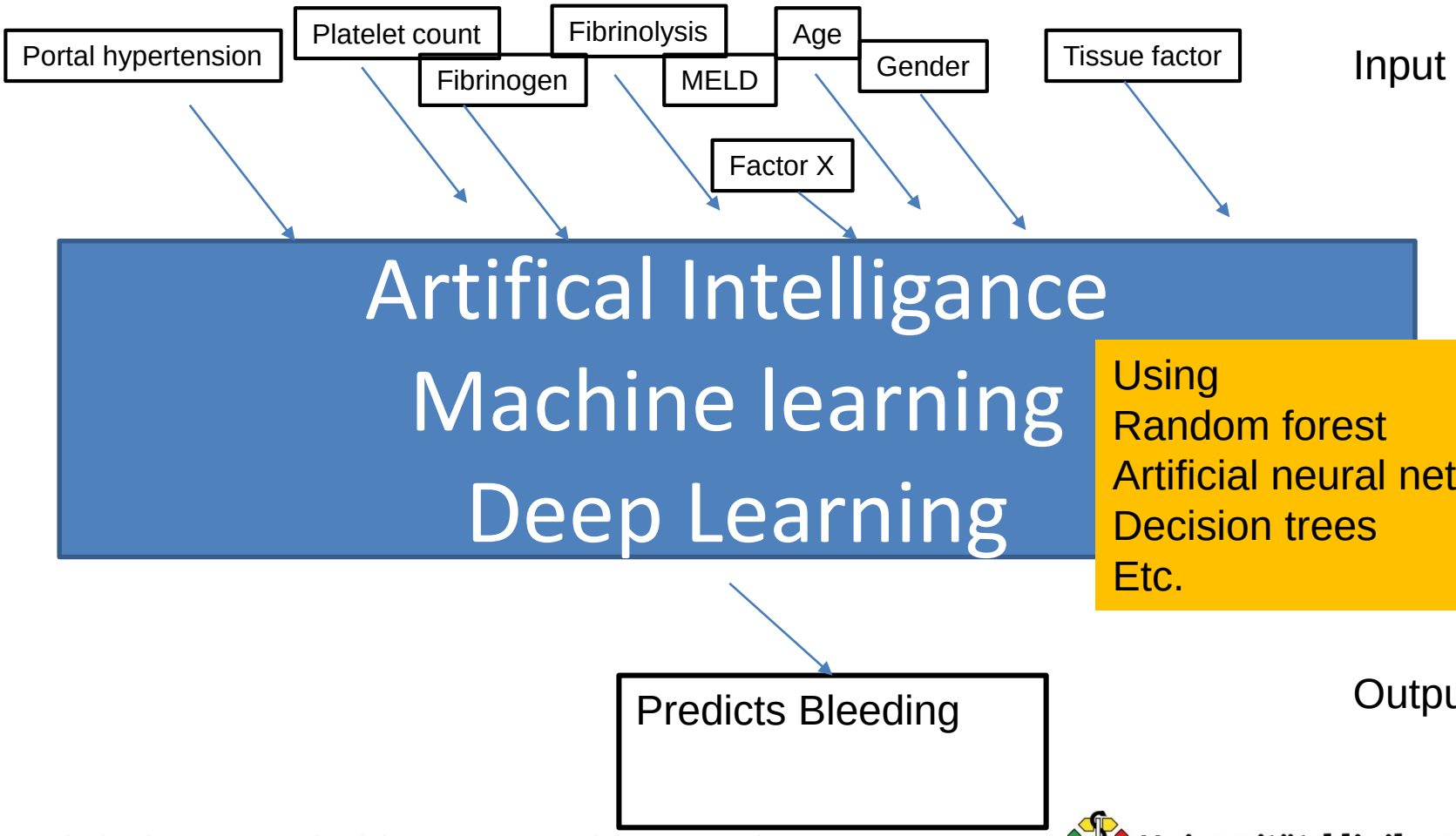
Universitätsklinikum Essen

Can we forecast bleeding?

- ROTEM/TEG assessment results in a higher transfusion threshold
- Primarly clinical use VET for intra-/postop to guide coagulation management
- Question: what are the lower limits of TEG/ROTEM preprocedural?
- No studies about predicting bleeding for invasive procedure

What brings us the future?

Time to change the classical vision of coagulation in liver disease: from the balance dysequilibrium to the systems biological network modelling



Blasi, Minerva Anaesthesiol, 2017, Dec 13. doi: 10.23736/S0375-9393.17.12313-8

Quotation of Max Planck

"A new scientific truth does not prevail in such a way that its opponents are convinced and taught to be learned, but rather by the fact that their opponents are gradually becoming extinct and that the adolescent generation is acquainted with the truth in advance."

Max Planck, 1858-1947

In 1919 he was awarded the Nobel Prize for Physics of the Year 1918 for the discovery of Planck's quantum of action

Oncologic outcomes

- Several reasons for inferior outcome after liver resection
  - Suboptimal resection
  - Postop complictaion
  - Transfusion with possible immunmodulatory and inflammatory effect
  - Retrospective study with 5 yr follow-up

Hallet, Ann Surg Oncol, 2015, DOI10.1245/s10434-015-4477-4