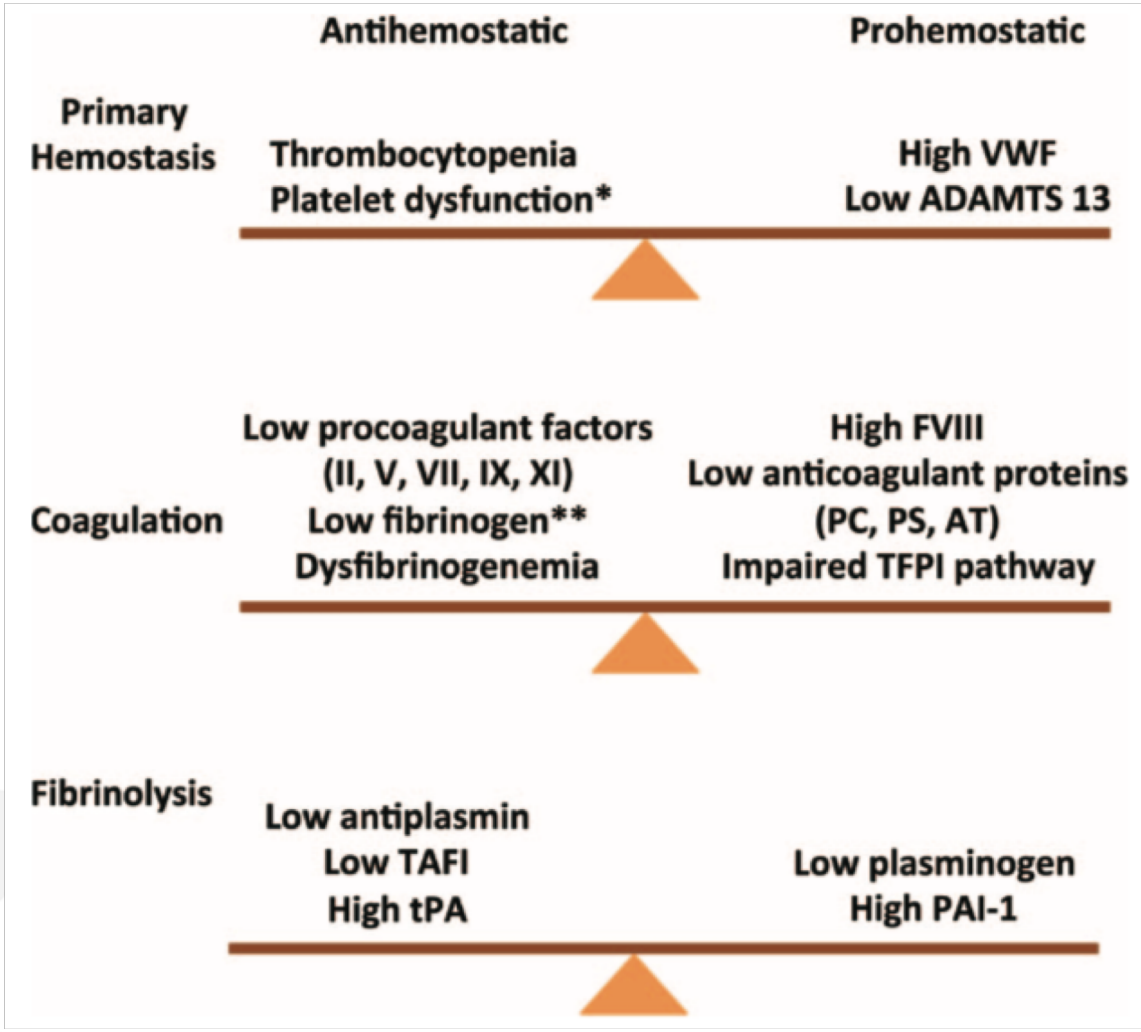
Coagulopathy of Liver Disease assessed by ROTEM and CAT

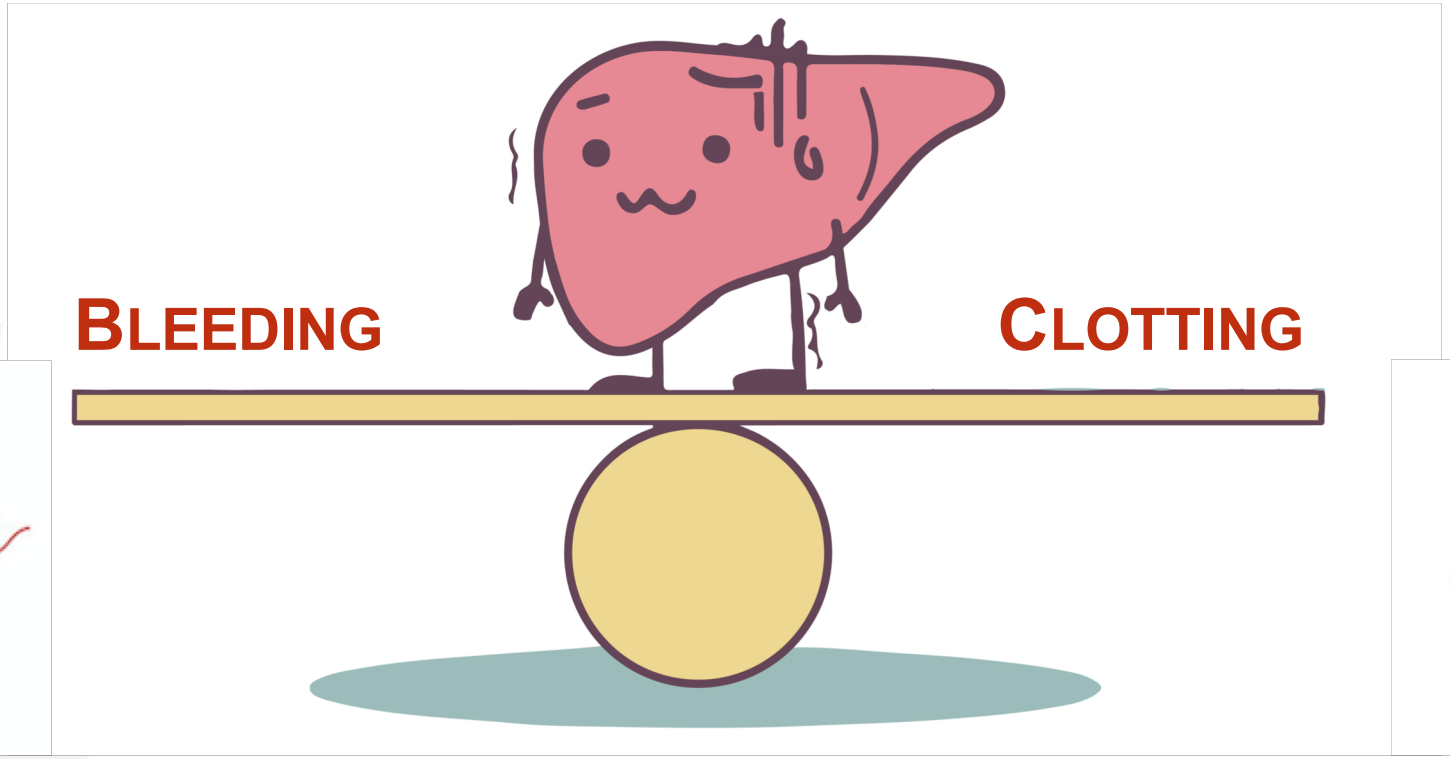
Sara Ng

”Re-balanced” haemostasis



Kujovich JL (ASH 2015)

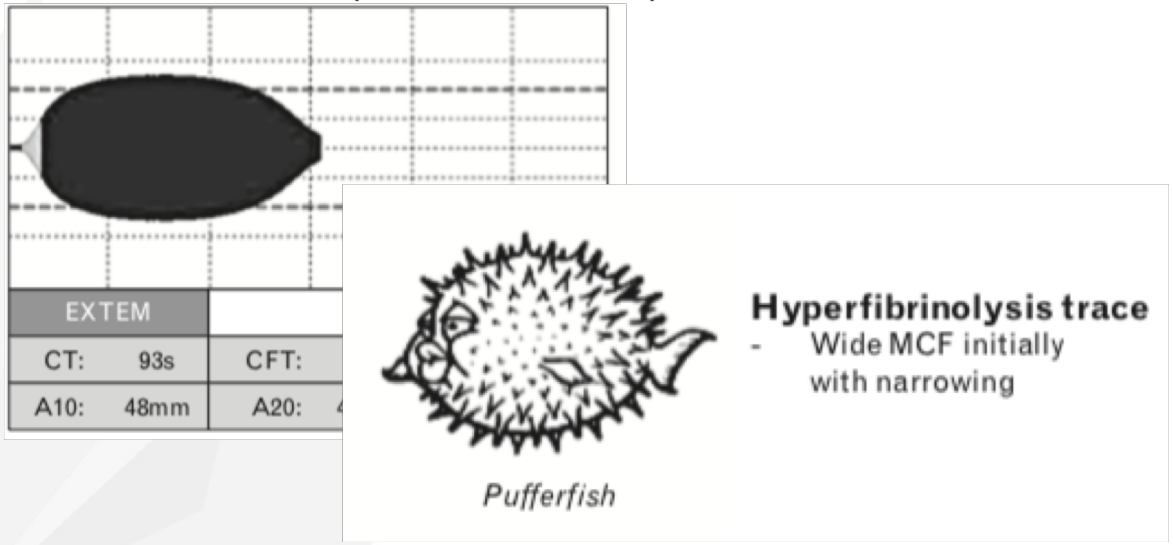
Why does it matter?



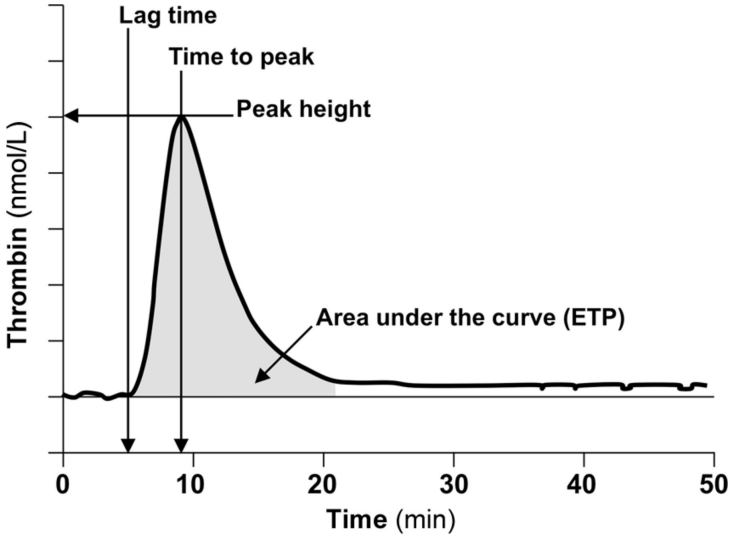
Coagulation Assays

Conventional coagulation assays
(PT, APTT, Platelet count*)

Viscoelastic Coagulation Assays
(ROTEM/TEG)



Calibrated Automated Thrombogram

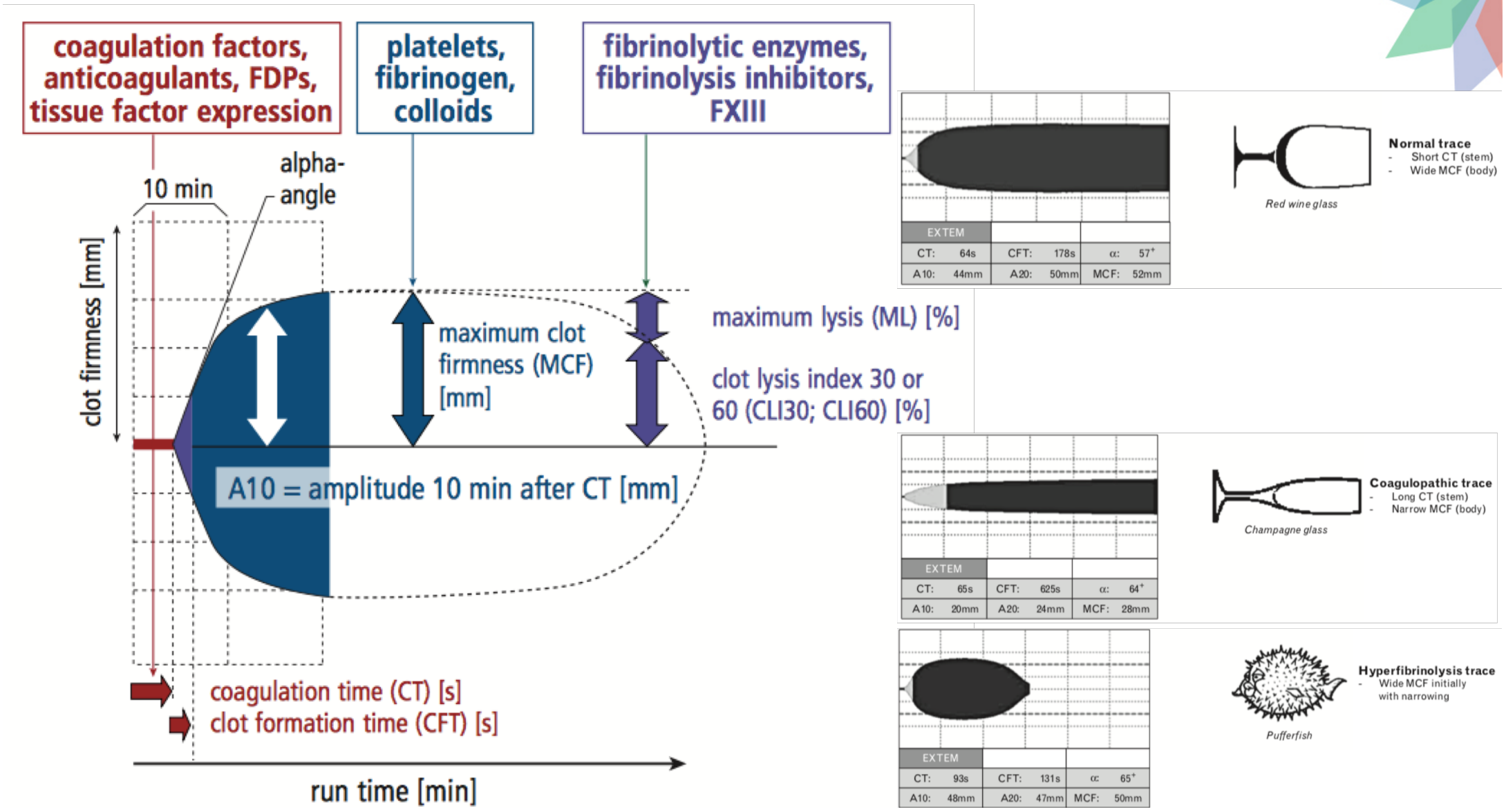


Rotational Thromboelastometry

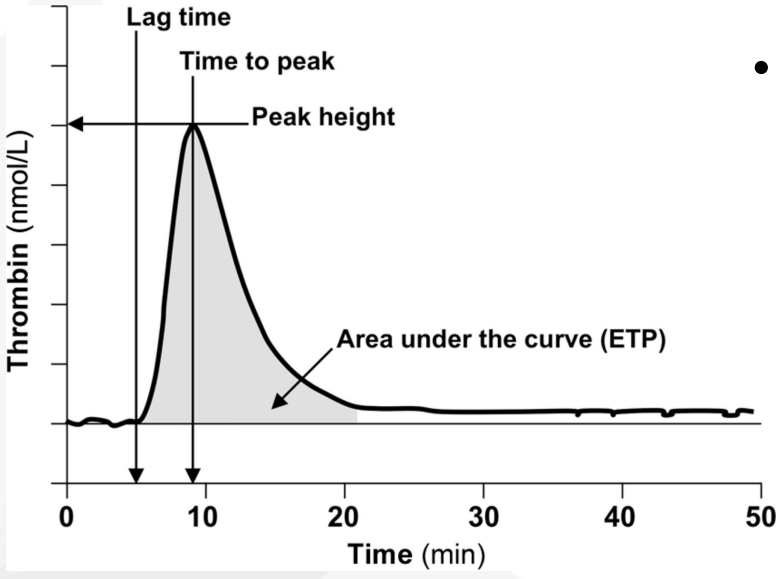
(ROTEM)

- A POCT measuring the viscoelastic properties of whole blood.
- Each test is initiated by recalcification of a citrated blood sample and by adding activators of the extrinsic and intrinsic pathways

  - **EXTEM** – Tissue factor
  - **FIBTEM** – Tissue factor + Cytochalasin D
  - **APTEM** – Tissue factor + Tranexamic acid
  - **INTEM** – Ellagic acid
  - **HEPTEM** – Ellagic acid + Heparinase


coagulation factors, anticoagulants, FDPs, tissue factor expression
platelets, fibrinogen, colloids
fibrinolytic enzymes, fibrinolysis inhibitors, FXIII
10 min
alpha-angle
clot firmness [mm]
maximum clot firmness (MCF) [mm]
maximum lysis (ML) [%]
clot lysis index 30 or 60 (CLI30; CLI60) [%]
A10 = amplitude 10 min after CT [mm]
coagulation time (CT) [s]
clot formation time (CFT) [s]
run time [min]
EXTEM
CT: 64s
CFT: 178s
α: 57+
A10: 44mm
A20: 50mm
MCF: 52mm
Red wine glass
Normal trace
- Short CT (stem)
- Wide MCF (body)
EXTEM
CT: 65s
CFT: 625s
α: 64+
A10: 20mm
A20: 24mm
MCF: 28mm
Champagne glass
Coagulopathic trace
- Long CT (stem)
- Narrow MCF (body)
EXTEM
CT: 93s
CFT: 131s
α 65+
A10: 48mm
A20: 47mm
MCF: 50mm
Pufferfish
Hyperfibrinolysis trace
- Wide MCF initially with narrowing

Calibrated Automated Thrombogram



- Thrombin generation was measuring using the method described by Hemker *et al*.
  - PPP + Trigger solution (TF, phospholipids, PPP reagent) + Fluka solution ($CaCl_2$, fluorogenic thrombin substrate)
  - Fluorescence is then measured by an automated microtiter plate fluorometer at 37^{o}C
  - The Thrombinoscope software program is used to calculate thrombin activity using a calibrator to display thrombin activity against time in a thrombogram – lag time, thrombin generation velocity, peak thrombin concentration, ttPeak and ETP.

Objective

01

Primary objectives

To study the relationship between conventional coagulation assays, ROTEM and CAT in patients with coagulopathic liver disease.

To identify which (ROTEM) parameters may be predictive of bleeding in this patient cohort.

Methods

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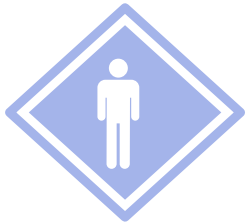


Twenty adult patients with cirrhotic liver disease admitted consecutively to Liverpool Hospital over a 6-months period (Nov 17 – Apr 18).

Eligible if INR ≥ 1.8 and/or platelets ≤ $50x10^9$/L.
Exclusion criteria were haemostatic disorders other than liver disease and the use of medications known to affect blood coagulation (antiplatelets and/or anticoagulant therapy).

Two sodium citrate tubes collected after informed consent.

- Tube #1: ROTEM
- Tube #2: PT/APTT/Fibrinogen & CAT

Results

Table 1 Patient demographics

	All (n=20)	Child-Pugh A (n=2)	Child-Pugh B (n=4)	Child-Pugh C (n=14)
Age (years)	58 (53-69)	73 (69-76)	70 (63-86)	56 (49-60)
Male sex *(n)*	13 (65%)	1 (50%)	2 (50%)	10 (71%)
Aetiology of liver disease* *(n)*				
HCV	4	1	1	4
HBV	2	0	0	2
Alcohol	11	0	1	10
NASH	4	0	2	2
Other^	4	2	1	1
Haemoglobin (120-170g/L)	98 (81-124)	99 (96-102)	112 (99-139)	93 (80-125)
Haematocrit (0.36-0.50L/L)	0.29 (0.24-0.36)	0.30 (0.28-0.31)	0.33 (0.30-0.41)	0.28 (0.24-0.36)
Platelets (150-400x10^9/L)	47 (41-69)	47 (46-48)	53 (43-111)	47 (37-72)
PT (12-15s)	24 (20-26)	18 (16-19)	16 (16-26)	24 (21-27)
INR (0.9-1.2)	2.1 (1.7-2.4)	1.5 (1.3-1.6)	1.7 (1.3-2.3)	2.2 (1.9-2.6)
APTT (25-37s)	44 (38-51)	36 (28-44)	40 (32-44)	47 (42-60)
Fibrinogen (2.0-4.3g/L)	1.8 (1.2-2.3)	2.0 (1.7-2.2)	2.6 (2.2-4.1)	1.3 (1.0-2.0)
D-dimer (<0.25mg/L)	1.80 (1.37-2.80)	0.95 (0.38-1.51)	1.77 (1.50-3.73)	1.93 (1.33-3.32)
Bilirubin (<21umol/L)	80 (31-131)	15 (13-17)	36 (18-102)	95 (24-199)
Albumin (33-48g/L)	37 (31-41)	37 (33-40)	43 (33-48)	35 (25-47)
MELD Score	23 (17-27)	16 (14-18)	20 (16-24)	25 (18-32)
Portal Hypertension *(n)*	19	2	3	14
Urea (3.0-8.0mmol/L)	7.7 (4.4-12)	13.7 (9.3-18.1)	9.3 (5.0-11.9)	6.6 (4.2-12.2)
Creatinine (45-110umol/L)	87 (66-136)	161 (116-206)	100 (62-88)	83 (67-132)
History of bleeding *(n)*	12	1	1	10
History of thrombosis *(n)*	8	1	4	3

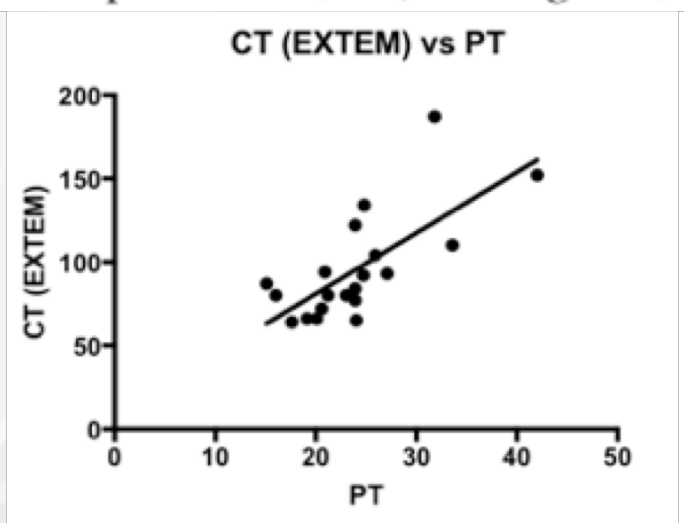
Values expressed as median with interquartile ranges

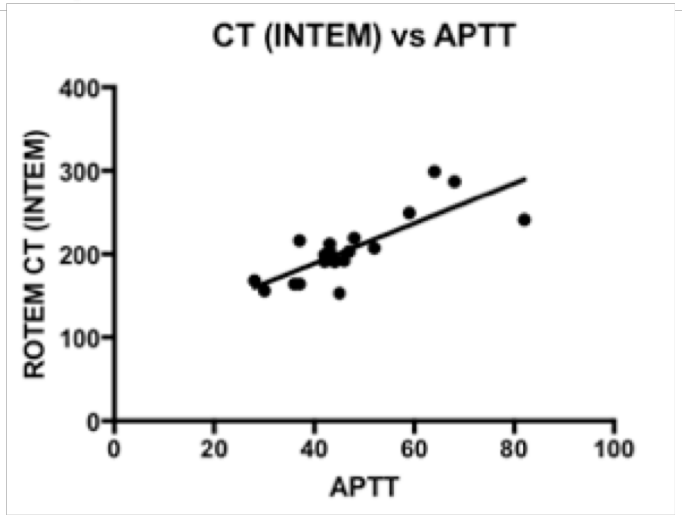
Results

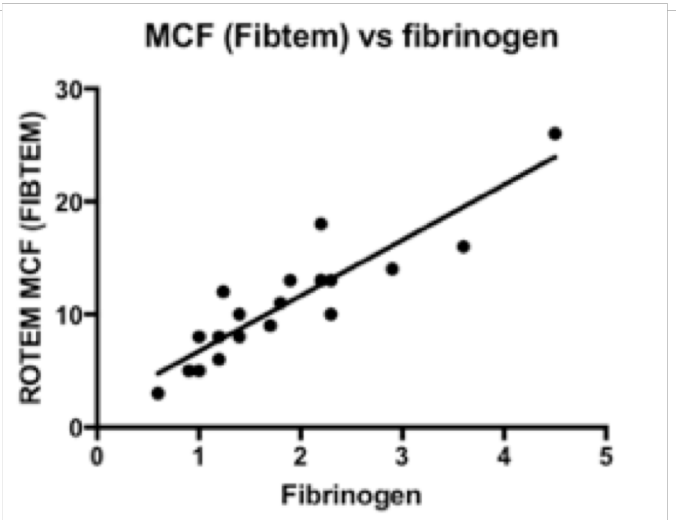
Table 2 Correlation between conventional coagulation and ROTEM parameters

Conventional coagulation parameters	ROTEM parameters	Correlation coefficient	*p*-value
PT (s)	CT_{EXTEM} (s)	0.71	0.0004
	CFT_{EXTEM} (s)	0.58	0.0104
APTT (s)	CT_{INTEM} (mm)	0.79	<0.0001
	CFT_{INTEM} (mm)	0.46	0.0392
Fibrinogen (g/L)	MCF_{FIBTEM} (mm)	0.90	<0.0001

Abbreviations: PT, Prothrombin time; INR, International Normalised Ratio, APTT, Activated partial thromboplastin time; CT, Clotting time; MCF, Maximum clot firmness





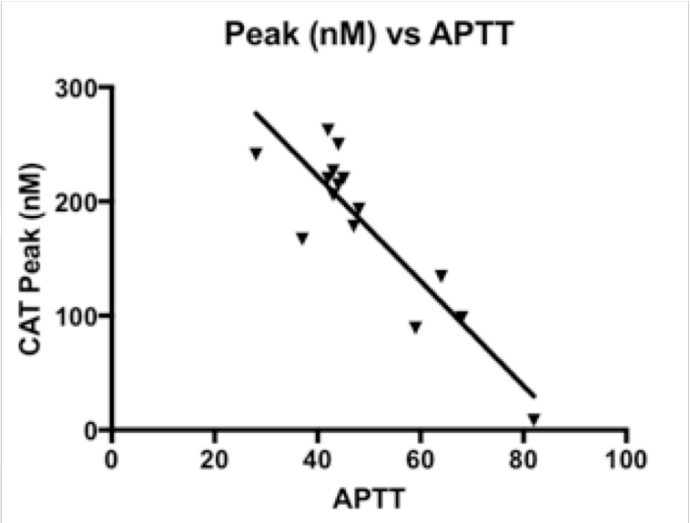


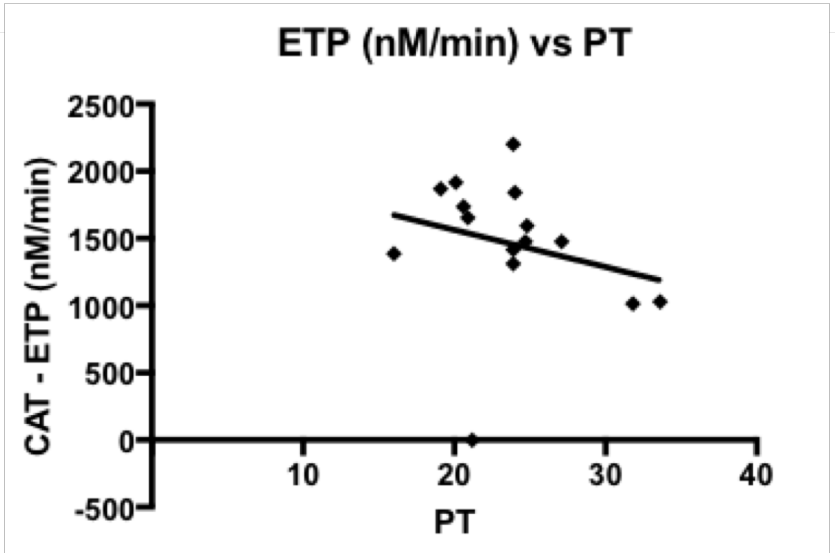
Results

Table 4 Correlation between conventional coagulation and CAT parameters

Conventional coagulation parameters	CAT parameters	Correlation coefficient	*p*-value
PT (s)	Peak thrombin (nM)	-0.79	0.0007
APTT (s)		-0.79	0.0007
PT (s)	ETP (nM/min)	-0.59	0.0270
Fibrinogen (g/L)	Lag time (min)	0.54	0.0471

Abbreviations: PT, Prothrombin time; APTT, Activated partial thromboplastin time; CAT, Calibrated automated thrombogram; ETP, Endogenous thrombin potential





Results

Table 5 Correlation between ROTEM and CAT parameters

ROTEM parameters	CAT parameters	Correlation coefficient	*p*-value
α $angle_{EXTEM}$	Peak thrombin (nM)	0.70	0.0056
MCF_{EXTEM} (mm)		0.66	0.0110
MCF_{INTEM} (mm)		0.66	0.0096
MCF_{FIBTEM} (mm)		0.52	0.0556
α $angle_{EXTEM}$	ETP (nM/min)	0.61	0.0214
MCF_{EXTEM} (mm)		0.59	0.0279
MCF_{INTEM} (mm)		0.58	0.0286
MCF_{FIBTEM} (mm)		0.57	0.0337

Abbreviations: CAT, Calibrated automated thrombogram; ETP, Endogenous thrombin potential; MCF, Maximum clot firmness

Results

- Platelet count showed poor correlation with measured ROTEM values.
- The calculated MCE (maximum clot elasticity, measured by MCF_{EXTEM}-MCF_{FIBTEM}), thought to be a more accurate estimate of the platelet contribution to overall clot firmness, did not correlate with platelet count.
- The contributory role of platelets was not measured in our CAT assays as PPP was used.

Results

Table 6 Laboratory values in patients with a bleeding history versus thrombotic history and in peri-procedural settings

	Bleeding (n=8)	**Thrombosis** (n=4)	**Peri-procedure** (n=9)
Age	54 (43-58)	70 (59-86)	57 (56-67)
MELD Score	24 (17-33)	20 (16-32)	24 (17-32)
Haemoglobin (120-170g/L)	87 (76-99)	99 (86-118)	93 (78-124)
Haematocrit (0.36-0.50L/L)	0.26 (0.23-0.29)	0.30 (0.26-0.35)	0.28 (0.23-0.36)
Platelets (150-400x10^9/L)	43 (38-63)	43 (38-57)	44 (39-65)
PT (12-15s)	24 (22-34)	22 (16-27)	24 (19-29)
INR (0.9-1.2)	2.2 (1.8-3.3)	1.9 (1.3-2.4)	2.1 (1.7-2.8)
APTT (25-37s)	45 (42-57)	40 (32-59)	48 (39-66)
Fibrinogen (2.0-4.3g/L)	1.1 (0.9-2.0)	2.3 (1.5-2.8)	1.4 (1.1-2.3)
MCF_{EXTEM} (56-72mm)	36 (28-40)	38 (33-45)	38 (33-38)
MCF_{INTEM} (51-69mm)	37 (31-41)	39 (33-47)	37 (33-39)
MCF_{FIBTEM} (6-21mm)	9 (5-12)	13 (8-14)	8 (7-12)
MCF_{APTEM} (52-77mm)	35 (28-41)	38 (32-47)	37 (20-40)
$MCE_{EXTEM-FIBTEM}$	45 (33-54)	46 (40-67)	46 (42-51)
CT_{EXTEM} (50-80s)	97 (74-145)	90 (70-124)	94 (82-143)
CT_{INTEM} (161-204s)	204 (193-239)	188 (158-277)	207 (178-264)
CFT_{EXTEM} (46-149s)	301 (177-376)	278 (191-345)	269 (228-345)
CFT_{INTEM} (62-130s)	282 (183-444)	245 (179-318)	233 (216-363)
Lag time (3.0-3.3min)	2.3 (2.0-3.0)	3.2 (2.67-3.78)	2.4 (2.2-2.6)*
Time to peak thrombin (6.2-7.3min)	4.6 (4.0-5.3)	5.4 (5.1-5.7)	4.7 (4.5-5.1)*
Peak thrombin (245-355nM)	199 (89-263)	170 (134-206)	164 (107-245)*
ETP (1728-2327nM/min)	1524 (1014-2201)	1536 (1477-1595)	1624 (1159-2064)*

Values expressed as median with interquartile ranges

*Only 4 of the 9 patients who underwent invasive procedures had samples for measuring thrombin generation

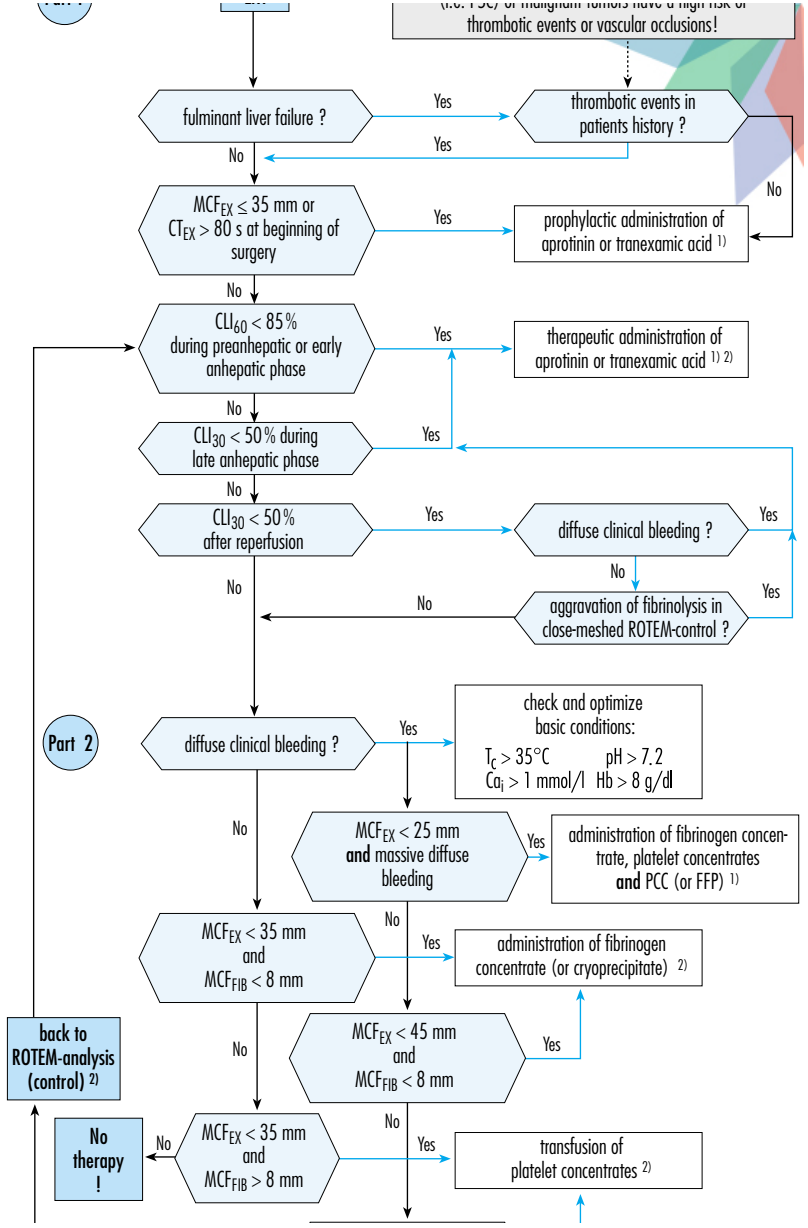
Discussion

- Poor correlation between PT and APTT with ROTEM-CT values have been previously quoted in the literature (r=0.24-0.37). However these studies were performed in patients undergoing liver transplantation (liver donors and recipients).

Discussion

- For the 9 patients who underwent invasive procedures, their ROTEM values satisfied the ROTEM-guided transfusion thresholds as suggested by Goerlinger's algorithm for coagulation management during liver transplantation.
    - 3 patients had prophylactic blood product transfusions

- There were no post-procedural bleeds with these targets, and whilst larger numbers are required to confirm this, it is possible that these ROTEM thresholds could be lowered and re-evaluated.



Limitations

- Small number of patients
- PRP would be a more physiological medium to measure thrombin generation.
- None of these assays take into account the role of the endothelium in haemostasis
- None these assays detect the activity of anticoagulants.

Acknowledgements

- Dr Penelope Motum
- Dr Minh Hua
- Sarah Just
- Diane Zebeljan
- Gastroenterology Department, Liverpool Hospital
- Laboratory staff at SWAPS Pathology, Liverpool Hospital