Predicting the risk of clinically relevant non-portal hypertension bleeding in patients with decompensated liver cirrhosis

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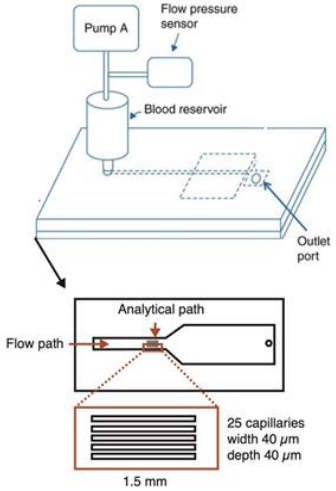
No conflict of interest

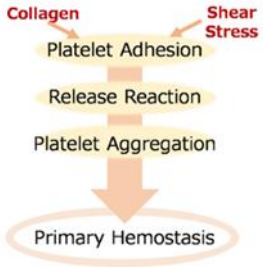
Introduction

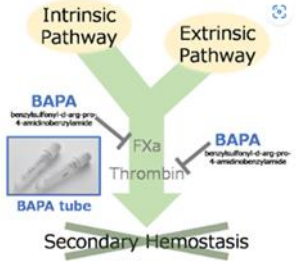
- Rebalanced hemostasis
- Fragile balance in decompensated cirrhosis
- Need of assays to predict clinically relevant bleeding
- Two new point-of-care laboratory methods of interest
  - → the Total Thrombus formation Analysis System (T-TAS)
  - → the Quantra hemostasis system (Quantra)

Total Thrombus-formation Analyzing System (T-TAS)

- Micro-chip flow-chamber based system
- PL-chip coated with collagen + anticoagulant binding Thrombin &FXa
- HD-chip coated with collagen and tissue factor
- Measure as Area under the pressure curve, AUC

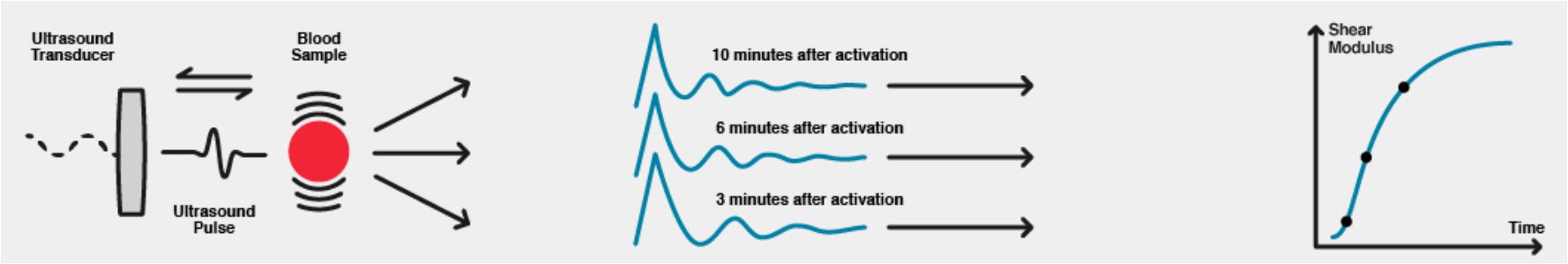






Quantra Analysing System (Quantra)

- Viscoelastic test on whole blood
- Ultrasound to create motion and create a clot
- Several hemostatic parameters
- Measures clotting time in s,



Aim

- Evaluate two novel point-of-care assays (T-TAS and Quantra) for their ability to predict clinically relevant non-portal hypertension bleeding in patients with decompensated cirrhosis.

Method

Non-portal hypertension bleeding

Follow up:
-Discharge
or
-28 days

Inclusion

ROTEM
Quantra
T-TAS

Decompensated liver cirrhosis (n=120)

Method

Non-portal hypertension bleeding

Follow up:
-Discharge
or
-28 days

Inclusion

ROTEM
Quantra
T-TAS

Decompensated liver cirrhosis (n=120)

Non-acute decompensation (NAD)
n=39

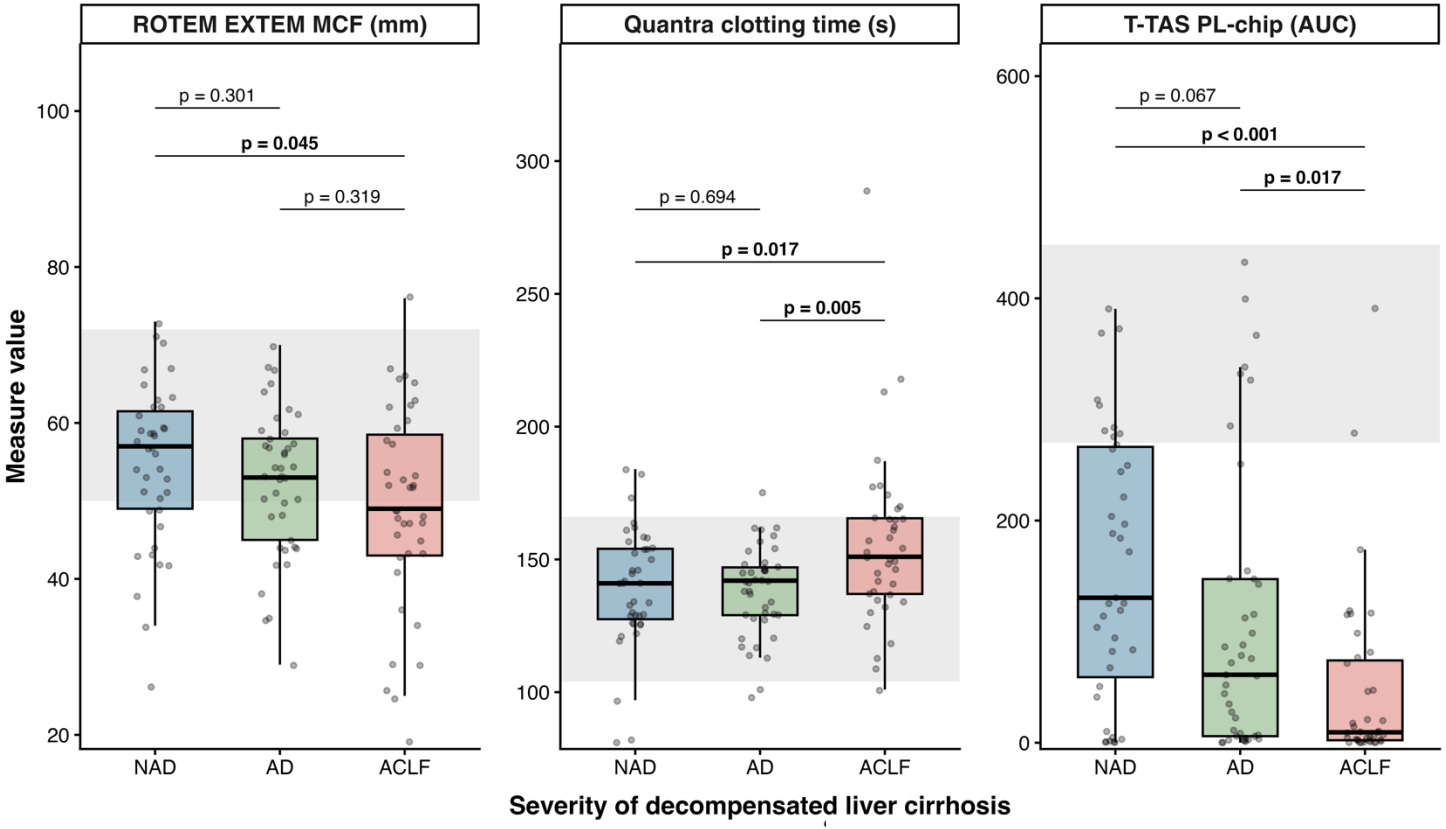
Acute decompensation (AD)
N=42

Acute-on-chronic liver failure (ACLF)
N=39

Baseline patient characteristics			
Characteristic	NAD (n=39)	AD (n=42)	ACLF (n=39)
Sex (Male %)	27 (69%)	24 (57%)	25 (64%)
Age, years (median (IQR))	63 (59–70)	60 (53–68)	59 (52–64)
Child Pugh (A/B/C)	1/20/18	0/13/29	0/8/31
MELD Na (points, median (IQR))	17 (11–20)	21 (15–25)	31 (26–38)
Bleeding (%)	1 (3%)	3 (7%)	13 (33%)

Novel haemostatic assays

Comparison between different stages of decompensated liver cirrhosis (grey area indicate normal range)



Clinically relevant non-portal hypertension bleeding

- 17 bleedings
- 9 major and 8 clinically relevant non-major bleeding
- 6 procedural bleedings

Patient Characteristics Stratified by Bleeding Status

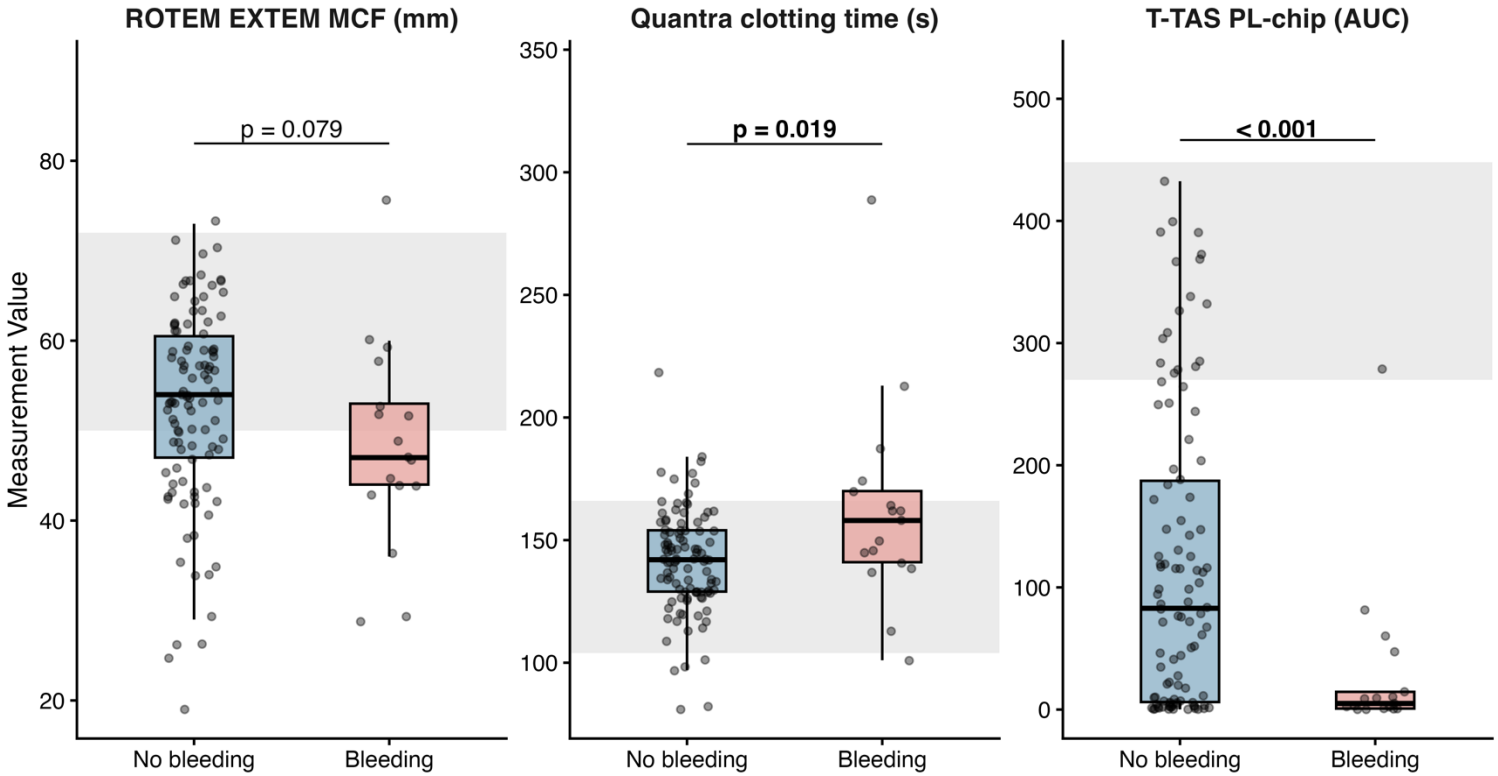
Comparing patients with and without clinically relevant bleeding

Characteristic	Bleeding (n=17)	No Bleeding (n=103)
Sex (Male %)	13 (76%)	63 (61%)
Age, years (median (IQR))	55 (51–61)	61 (55–69)
Stage of Decompensation (NAD/AD/ACLF)	1/3/13	38/39/26
Child Pugh (A/B/C)	0/2/15	1/39/63
MELD Na (points, median (IQR))	36 (27–38)	20 (15–26)

Continuous variables: median (IQR). Categorical variables: n (%) or counts (NAD/AD/ACLF and A/B/C).

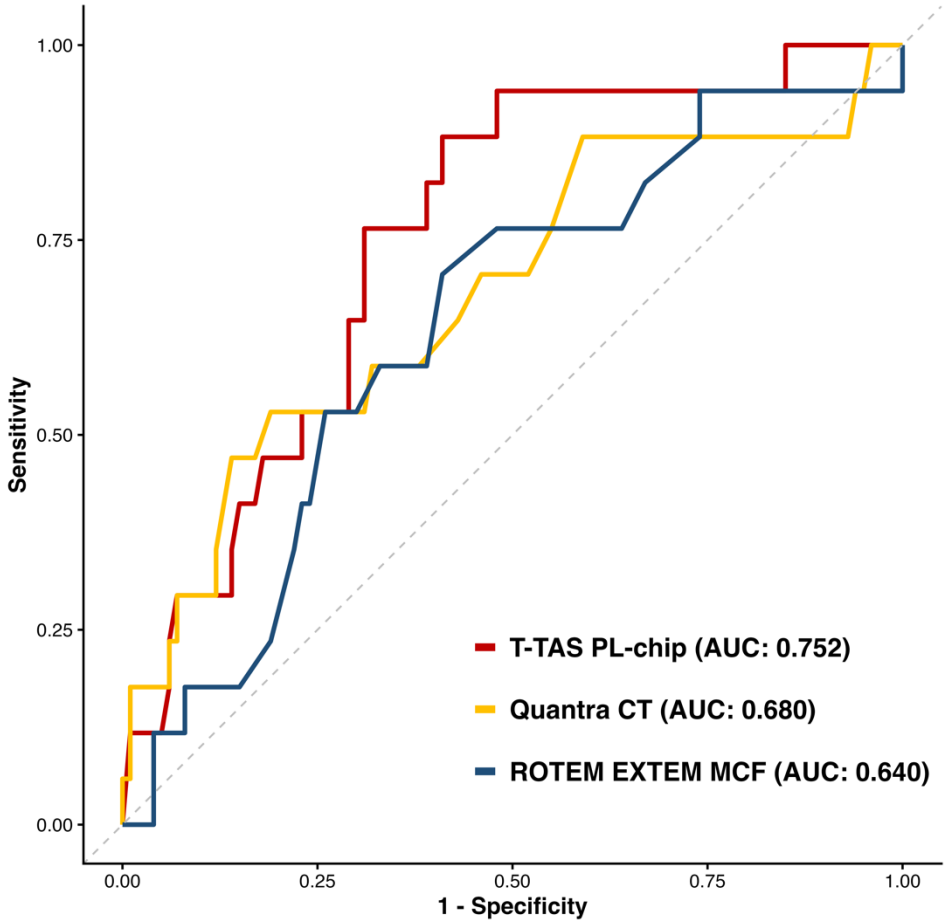
Clinically relevant non-portal hypertension bleeding

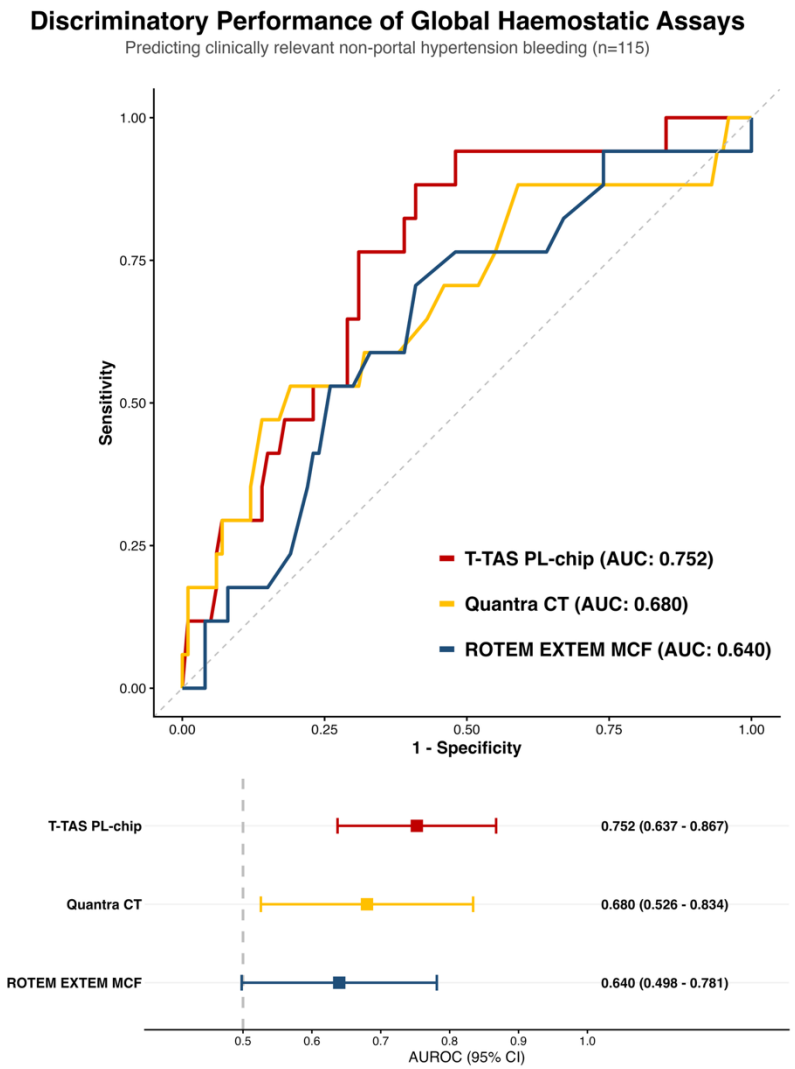
Comparison of haemostatic assays (grey area indicates normal range)



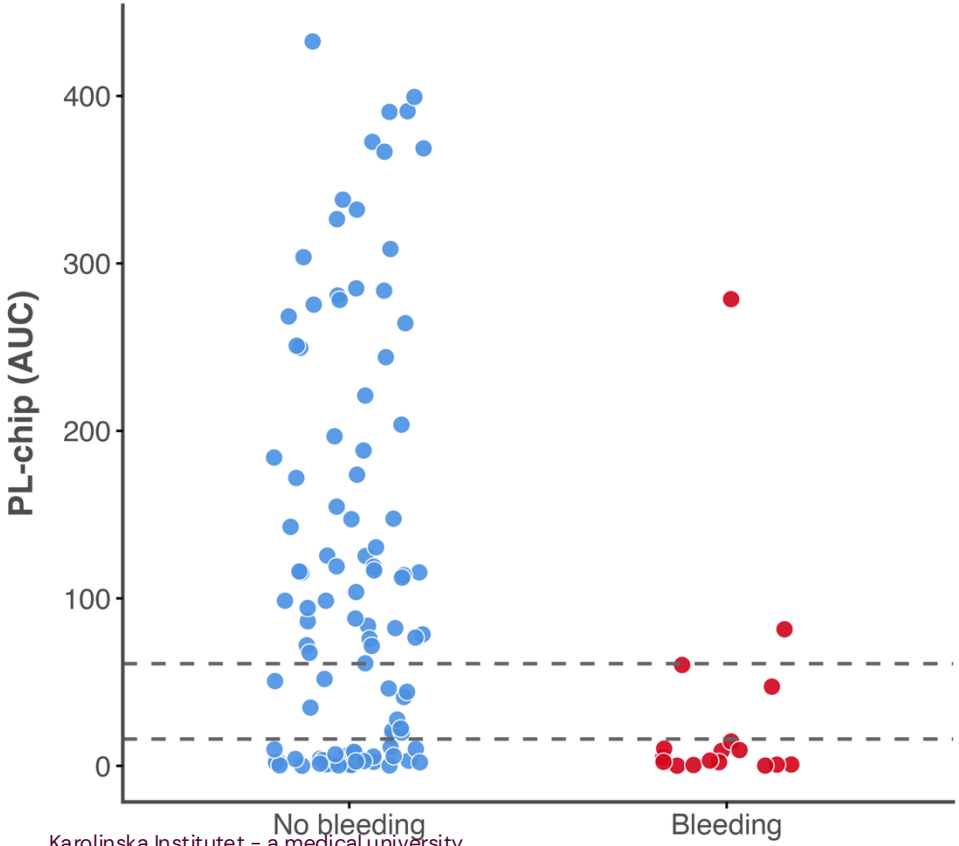
Discriminatory Performance of Global Haemostatic Assays

Predicting clinically relevant non-portal hypertension bleeding (n=115)




Discriminatory Performance of Global Haemostatic Assays
Predicting clinically relevant non-portal hypertension bleeding (n=115)
Sensitivity
1 - Specificity
0.00
0.25
0.50
0.75
1.00
T-TAS PL-chip (AUC: 0.752)
Quantra CT (AUC: 0.680)
ROTEM EXTEM MCF (AUC: 0.640)
T-TAS PL-chip
Quantra CT
ROTEM EXTEM MCF
0.752 (0.637 - 0.867)
0.680 (0.526 - 0.834)
0.640 (0.498 - 0.781)
0.5
0.6
0.7
0.8
0.9
1.0
AUROC (95% CI)

Relative risk of bleeding at different cut offs T-TAS PL-chip



Cut-off	Relative risk 95% CI	p-value
61[1]	7.89 (1.89 - 32.99)	< 0.001
16[2]	5.34 (1.86 - 15.39)	< 0.001

[1] *Calculated using Youden's Index.*

[2] *Calculated using the closest-to-(0,1) criterion.*

Conclusion

- T-TAS and Quantra have a better ability than currently often used ROTEM to discriminate for clinically relevant non-portal hypertension bleeding in decompensated liver cirrhosis

- A cut off at 61 AUC or below for the T-TAS PL-chip shows an 8 times higher relative risk of bleeding

- This needs to be validated in further studies.

Thank you to my supervisors and the Stål-Wahlin group

Per Stål
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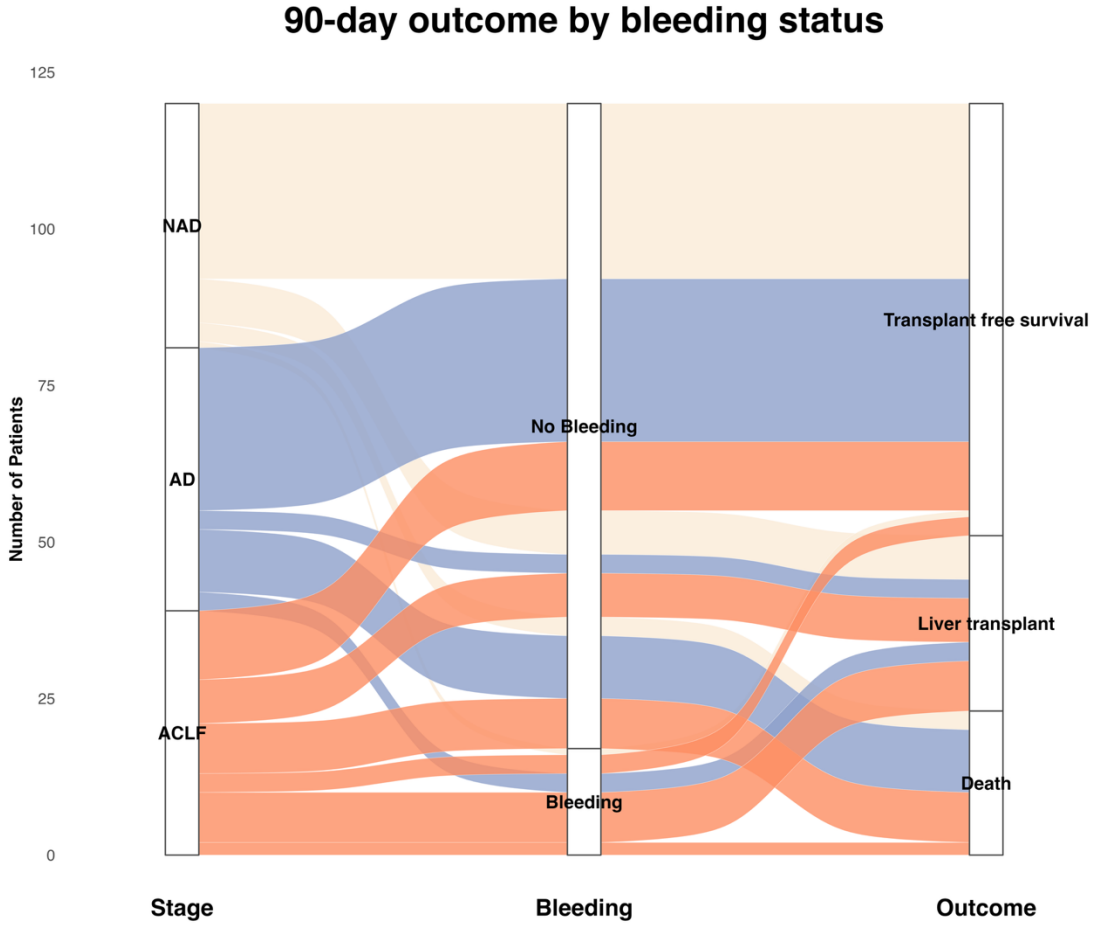
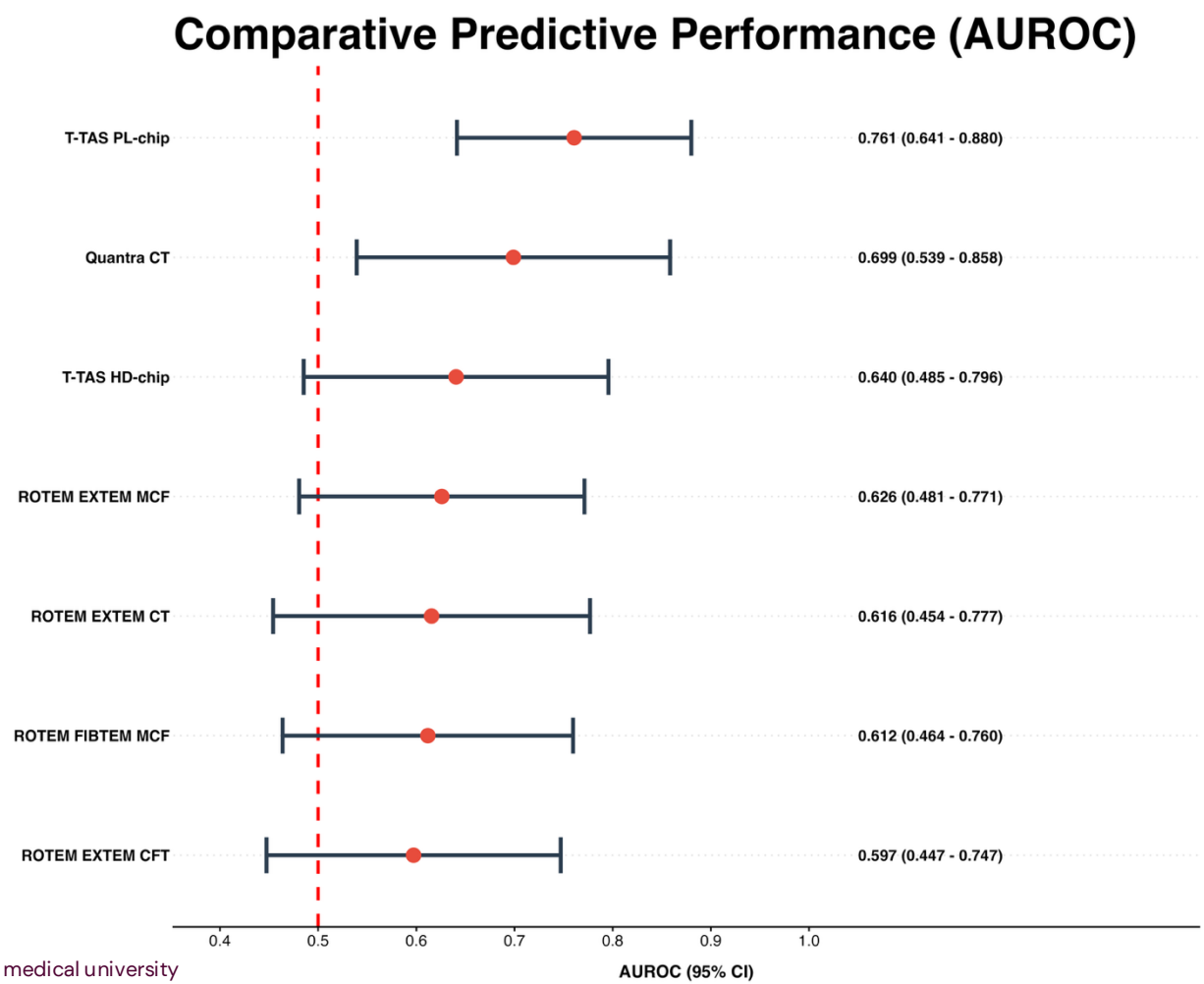
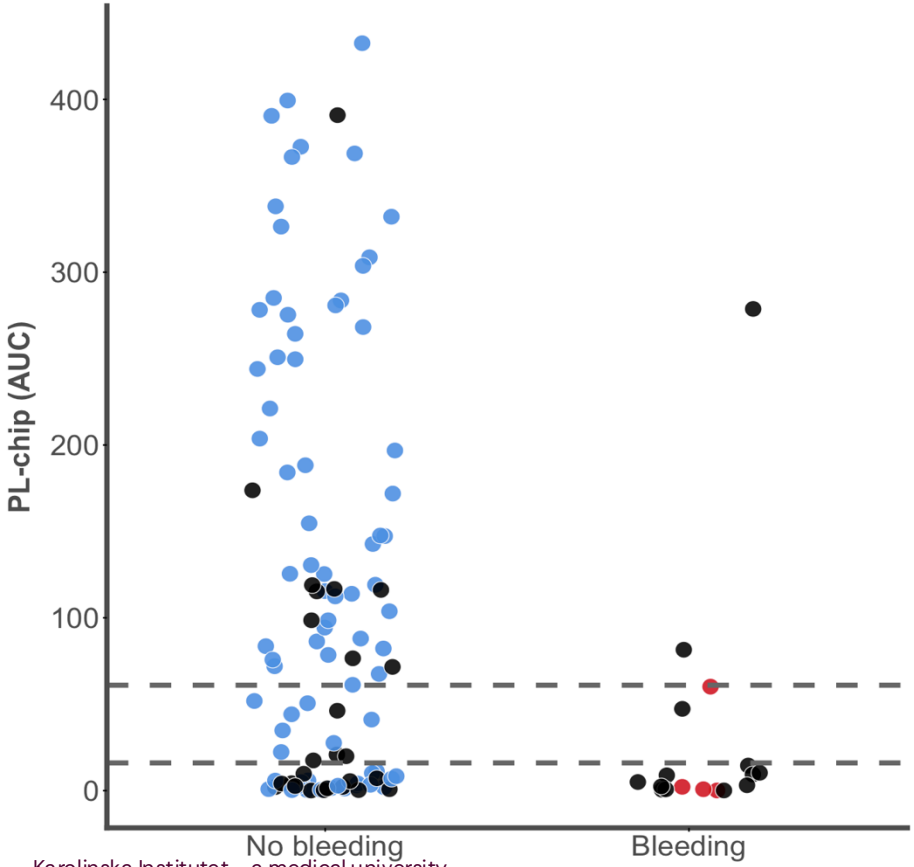
Staffan Wahlin
Gabriel Dumitrescu

Karolinska
Institutet


90-day outcome by bleeding status
125
100
75
50
25
0
Number of Patients
NAD
AD
ACLF
No Bleeding
Bleeding
Transplant free survival
Liver transplant
Death
Stage
Bleeding
Outcome


Comparative Predictive Performance (AUROC)
T-TAS PL-chip
0.761 (0.641 - 0.880)
Quantra CT
0.699 (0.539 - 0.858)
T-TAS HD-chip
0.640 (0.485 - 0.796)
ROTEM EXTEM MCF
0.626 (0.481 - 0.771)
ROTEM EXTEM CT
0.616 (0.454 - 0.777)
ROTEM FIBTEM MCF
0.612 (0.464 - 0.760)
ROTEM EXTEM CFT
0.597 (0.447 - 0.747)
0.4
0.5
0.6
0.7
0.8
0.9
1.0
AUROC (95% CI)

Relative risk of bleeding at different cut offs T-TAS PL-chip



Clinical Status / ACLF
- ACLF Patient
- Bleeding
- No bleeding

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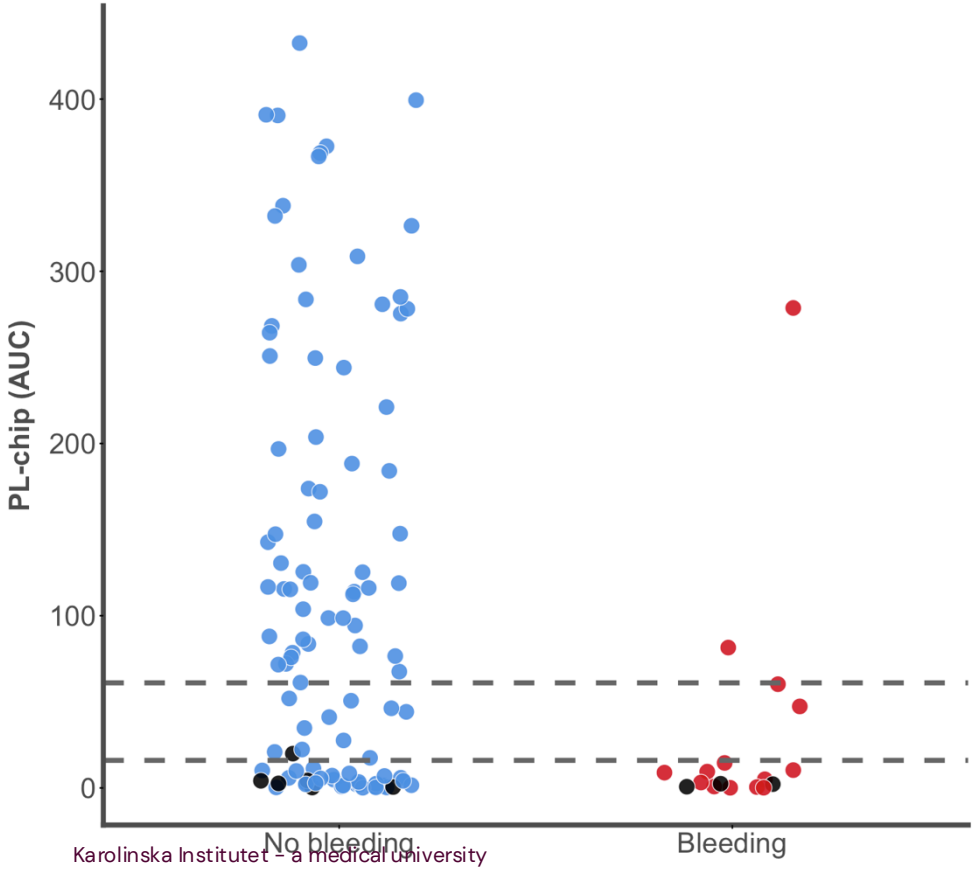

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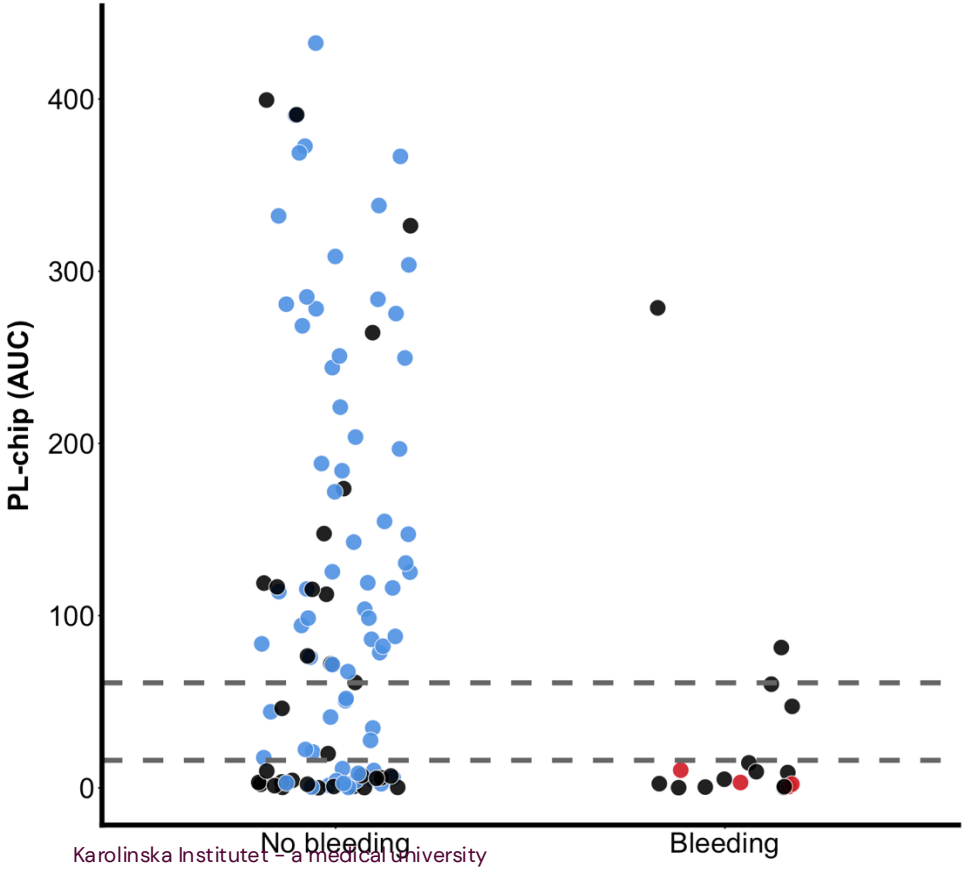
Relative risk of bleeding at different cut offs T-TAS PL-chip



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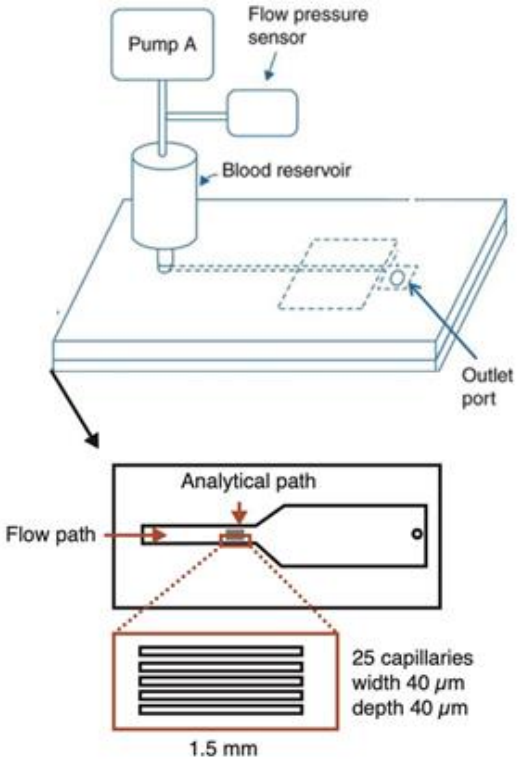
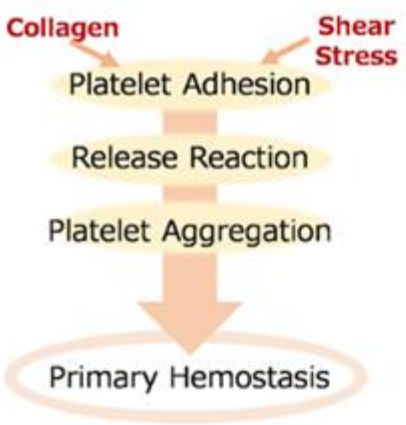
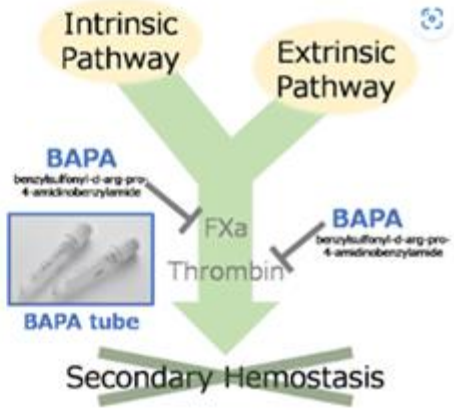
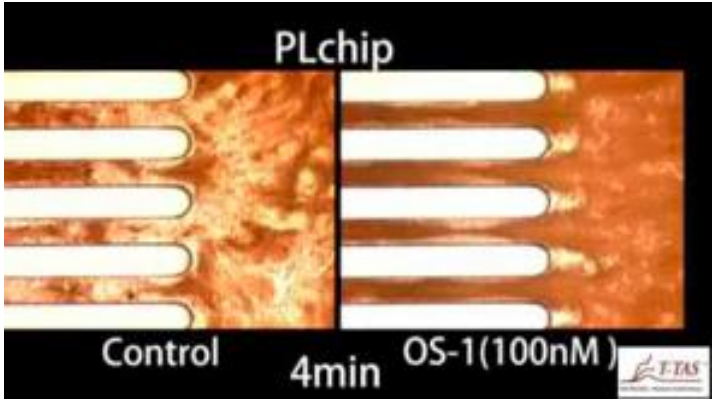

Pump A
Flow pressure sensor
Blood reservoir
Outlet port
Analytical path
Flow path
25 capillaries
width 40 μm
depth 40 μm
1.5 mm


Collagen
Shear Stress
Platelet Adhesion
Release Reaction
Platelet Aggregation
Primary Hemostasis

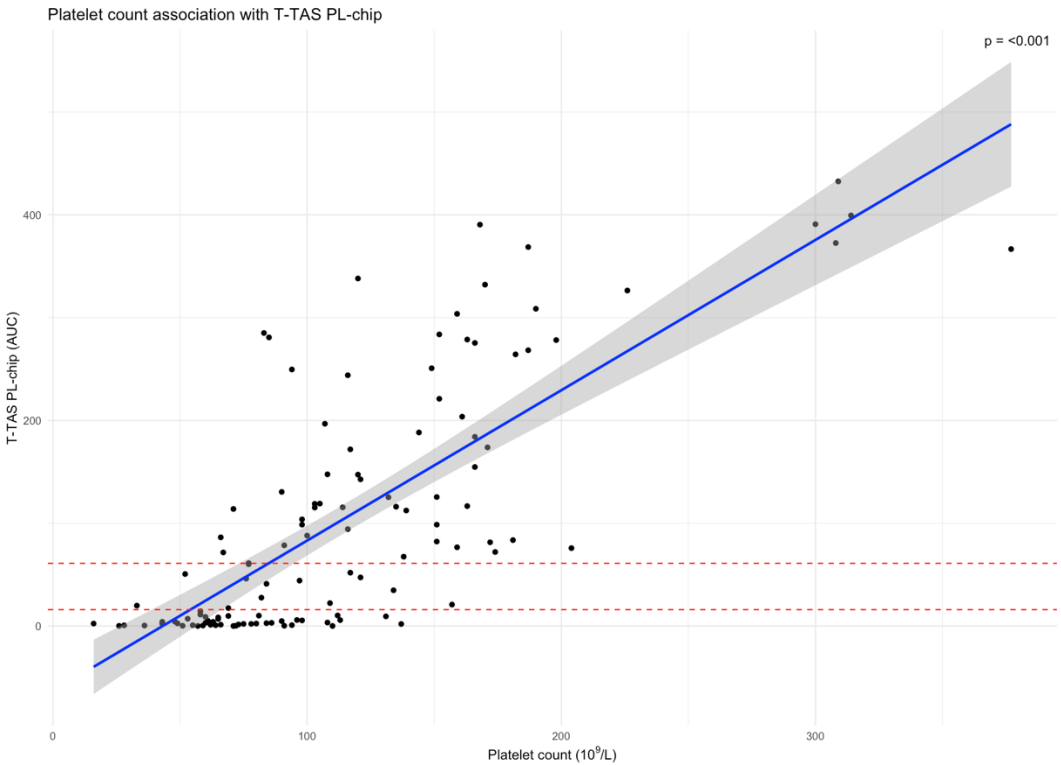

Intrinsic Pathway
Extrinsic Pathway
BAPA
BAPA
FXa
Thrombin
BAPA tube
Secondary Hemostasis

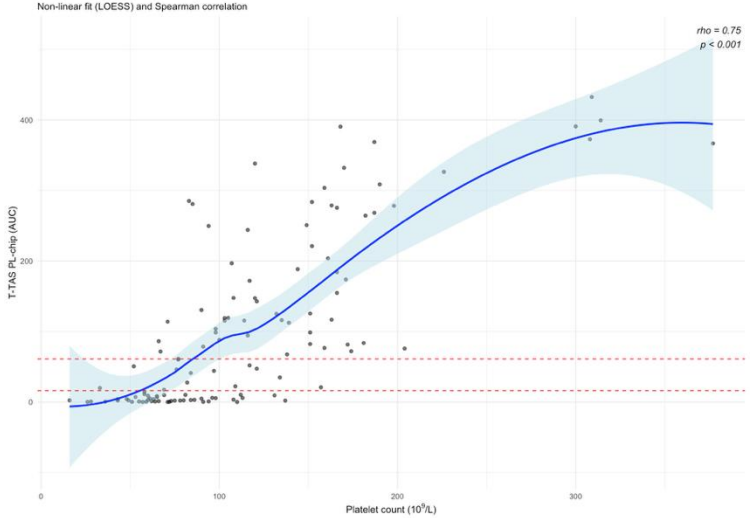

PLchip
Control
4min
OS-1(100nM)

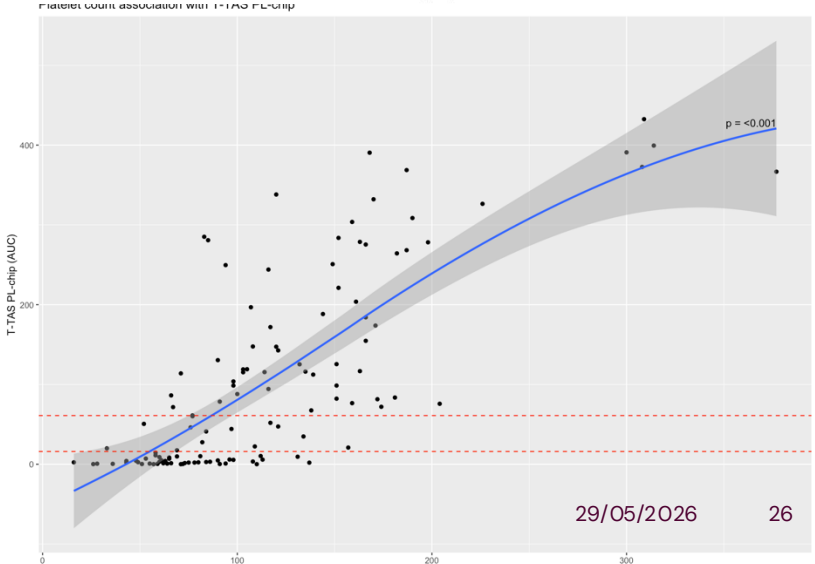
Quantra

- Clotting time (CT) (s)
- Clot stiffness (CS) (%)
- Fibrogen Clot Stiffness (FCS) (hPa)
- Platelet Clot Stiffness (PCS) (hPa)
- Clot stability to lysis (CSL) (%)

Platelets


Platelet count association with T-TAS PL-chip
p = <0.001
T-TAS PL-chip (AUC)
Platelet count (10^9/L)


Non-linear fit (LOESS) and Spearman correlation
rho = 0.75
p < 0.001
T-TAS PL-chip (AUC)
Platelet count (10^9/L)


p = <0.001
T-TAS PL-chip (AUC)