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ROTEM Area Under the Curve Predicts Major Non–Portal Hypertensive Bleeding in Acute-on-Chronic Liver Failure

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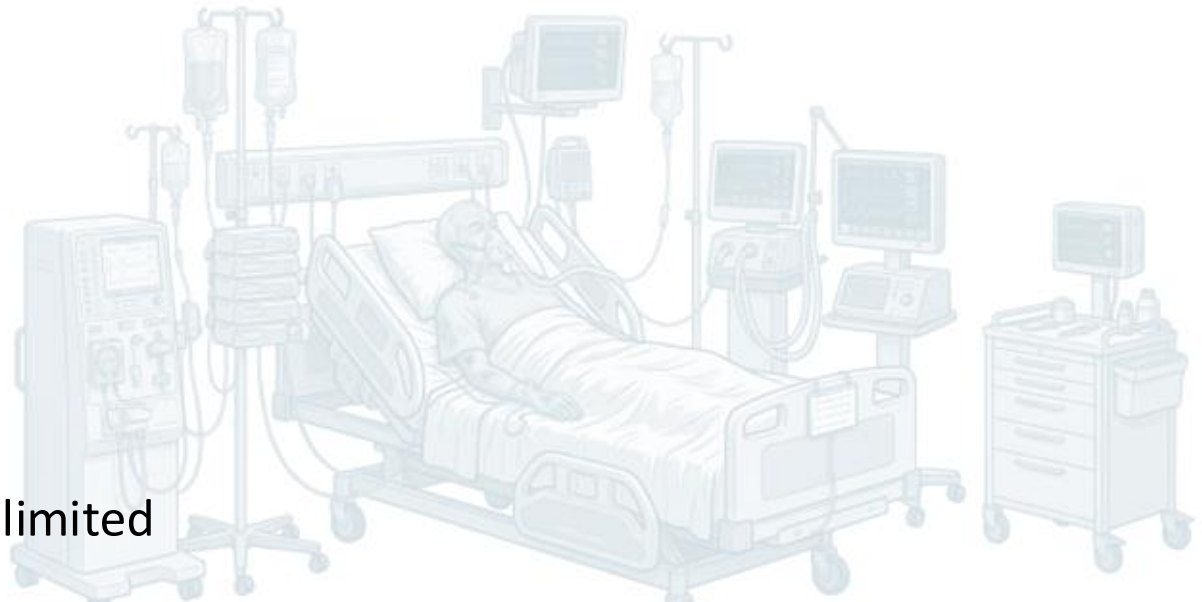
Introduction

Non–portal hypertensive (NPH) bleeding in ACLF

- Frequent and potentially life-threatening complication
- Includes:
  - spontaneous bleeding
  - post-procedural bleeding
- Reported prevalence varies widely (**7.35%–67%**)
- Major bleeding:
  - leading cause of clinical deterioration
  - associated with high morbidity
- Reliable identification of high-risk patients remains limited



Intagliata et al., *Gastroenterology*, 2023; Ferdinande et al., *Liver Int*, 2025.

Limitations of current coagulation testing

Traditional concept: ‘coagulation failure’

- Based on abnormal INR and PT
- Assumed to reflect bleeding tendency

However:

- Large meta-analysis (>13,000 patients):
  - no association between INR and bleeding risk
  - no difference between bleeders vs non-bleeders

Other parameters:

  - thrombocytopenia → inconsistent
  - hypofibrinogenemia → inconsistent

Plasma-based tests fail to reflect haemostatic status and association with bleeding

Kovalic et al., *APT*, 2020; Intagliata et al. *Gastroenterology*, 2023

Rotational thromboelastometry (ROTEM)

Whole-blood assessment

Current limitations in bleeding risk prediction

- Focus on isolated ROTEM parameters
- Inconsistent results (heterogenous patient population and bleeding definition)
- No data available on global haemostatic ROTEM metric

Concept of ROTEM Area Under the Curve (AUC)

- Integrates clot kinetics and firmness over time
- Represents global viscoelastic clot profile

Challenge

- Not available in current ROTEM platforms
- Requires mathematical derivation

Bihari et al., *Hepatol Int*, 2020; Campello et al. *Liver Int*, 2021

Study objectives

1) Develop method to calculate ROTEM AUC

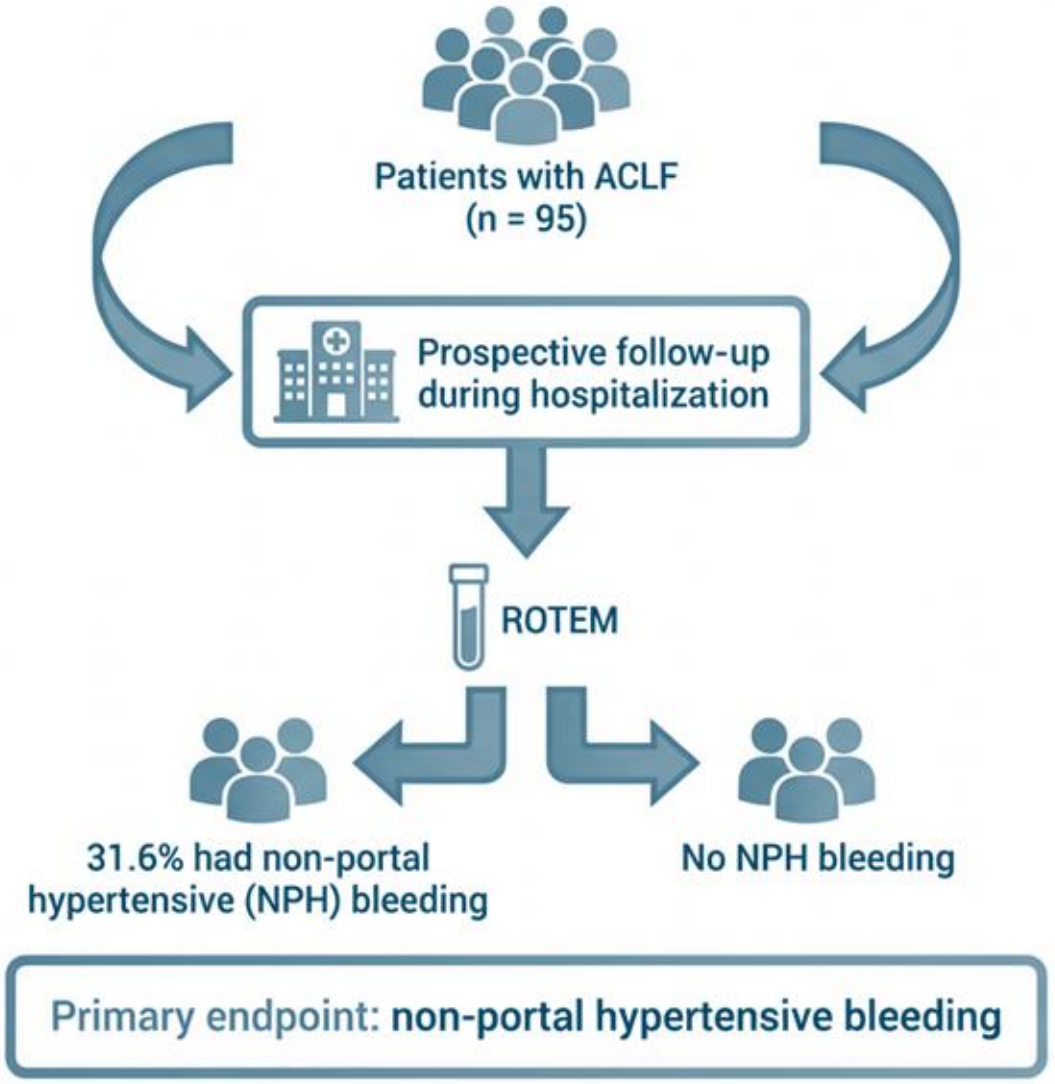
2) AUC validation and applying to total patient cohort

3) Evaluate discriminative ability for NPH bleeding

4) Assess independent association with NPH bleeding

5) Assess potential benefit in clinical NPH bleeding risk prediction

Study population



Design

- Multicentre cohort (Padova University Hospital, Ghent University Hospital, AZ Delta Hospital)
- Retrospective analysis of prospective data

Study population

- **Age** 59.7 yrs, 62% **male**
- **Liver disease severity:**

  → MELD 25, Child-Pugh 11, CLIF-C ACLF 47

  → ACLF grade I 71%, grade II 15%, grade III 14%
- **Aetiology:**

  → Alcohol 60%, MASLD 11%, Viral 10%, Other 19%
- Acute kidney injury 32%, bacterial infection 44%
- **Coagulation laboratory parameters**

  → INR 2.1, Fibrinogen 205 mg/dL, Platelets 84 $\times 10^9$/L, AT 36%

Study population: patients with vs without NPH-bleeding

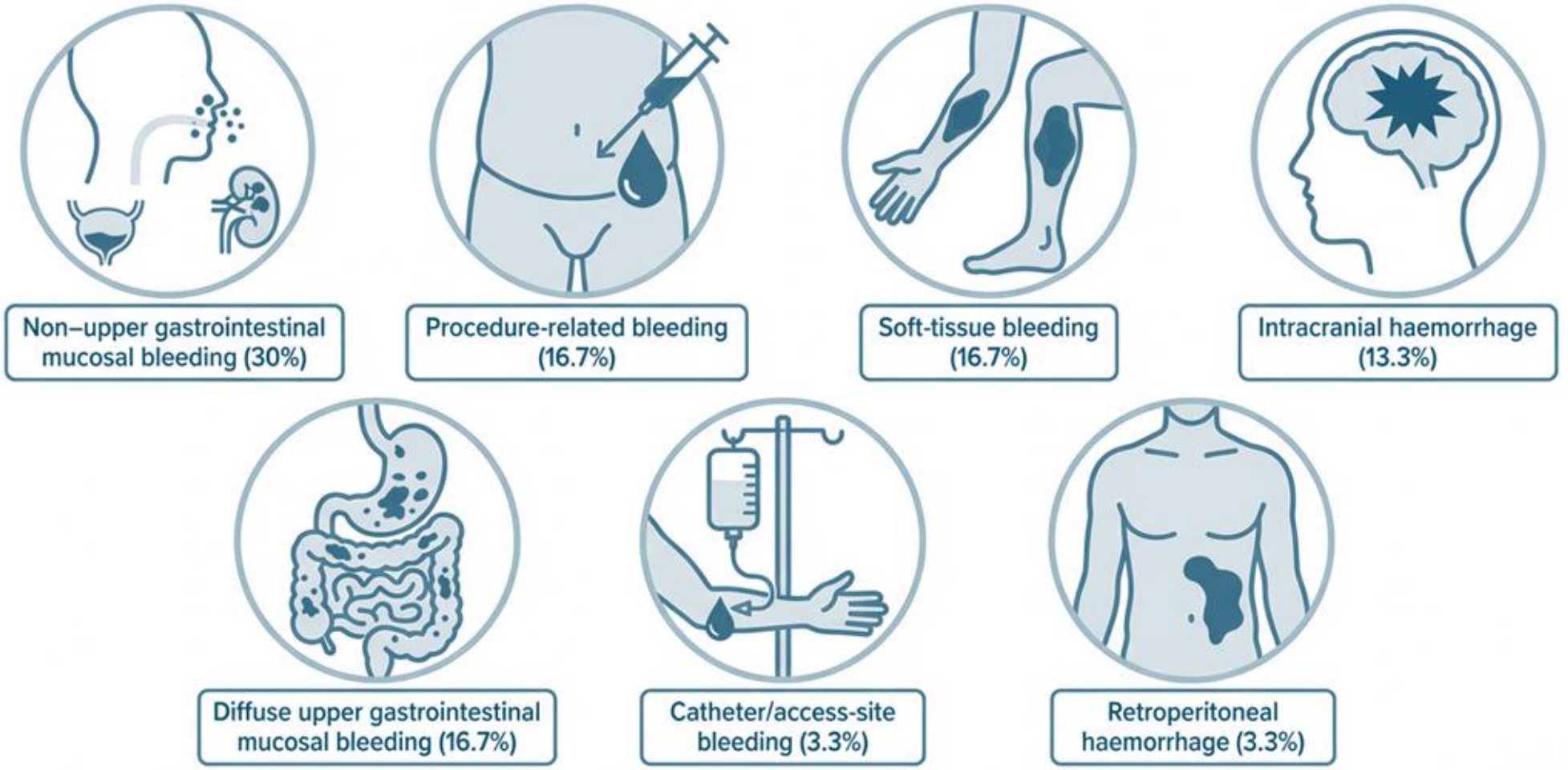
Significant difference observed for:

Variable	NPH-bleeding	No NPH-bleeding	p-value
MELD	29	23	0.003
Platelets	64.8	93.4	0.001
INR	2.5	1.9	0.002
Fibrinogen	181	215	0.018

No significant difference observed for:

- ACLF grade
- CLIF-C ACLF score
- Aetiology of cirrhosis
- Bilirubin
- Albumin

Types of NPH-bleeding



ROTEM AUC derivation and application

Methodological approach

- Multivariable linear regression

Final calculation

- AUC INTEM/EXTEM = 176.47 − 0.579 × TMCF − 0.346 × CT + 0.802 × CFT + 100.12 × MCF
- Agreement with reference AUC (available in 46 patients)
  - AUC INTEM: CCC 0.952
  - AUC EXTEM: CCC 0.955
  - → **Excellent concordance**
- Applied to full cohort for standardisation

Study population: patients with vs without NPH-bleeding

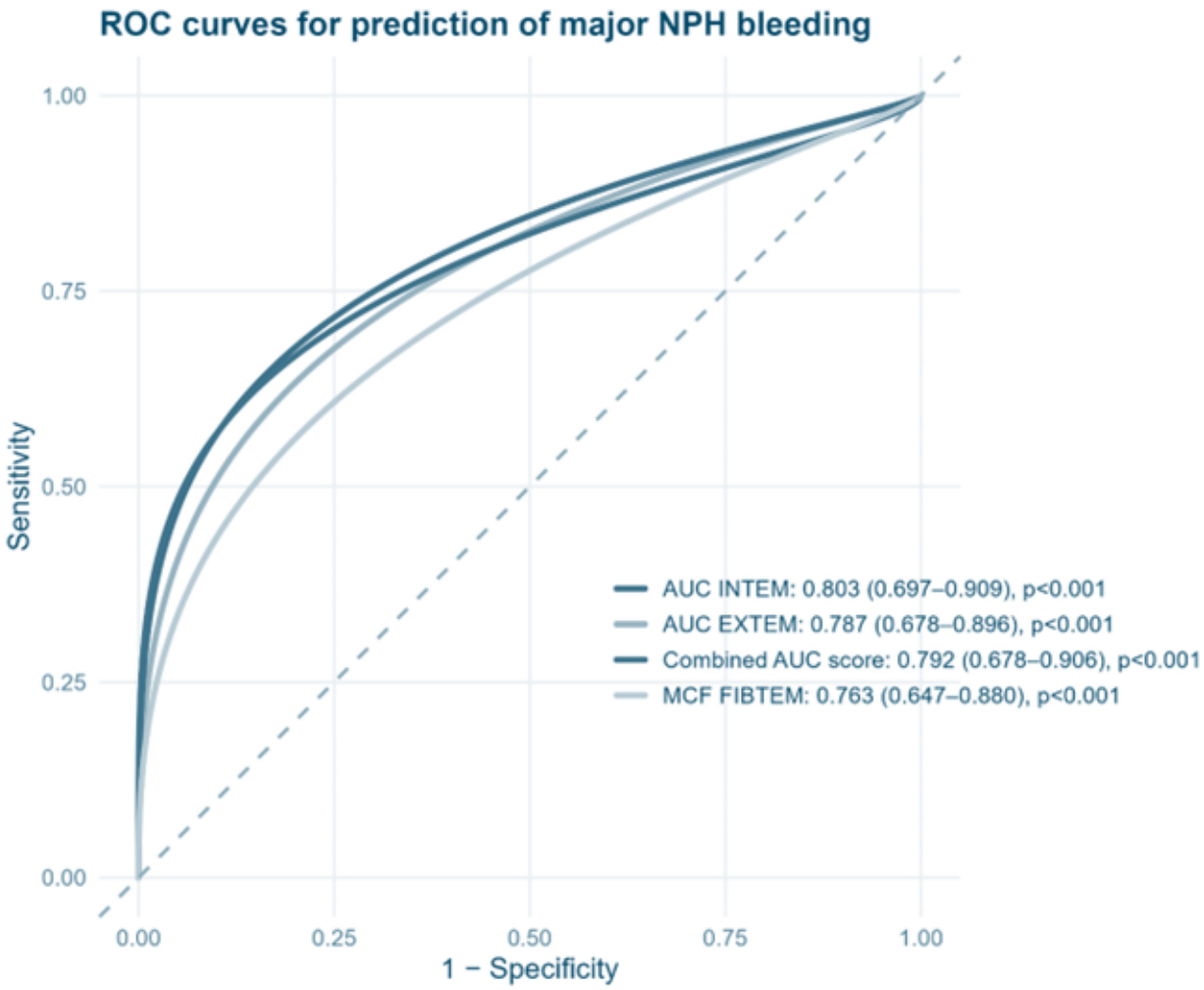
Parameter	NPH-bleeding	No NPH-bleeding	p-value
CT INTEM (s)	275.7	218.0	<0.001
CFT INTEM (s)	383.7	134.5	<0.001
MCF INTEM (mm)	35.8	48.2	<0.001
AUC INTEM (mm·s)	**3260.5**	**4528.7**	**<0.001**
CT EXTEM (s)	95.8	72.4	<0.001
CFT EXTEM (s)	334 (223)	139 (110)	<0.001
MCF EXTEM (mm)	37.4	50.0	<0.001
AUC EXTEM (mm·s)	**3627.5**	**4884.3**	**<0.001**
MCF FIBTEM (mm)	**7.8**	**12.7**	**<0.001**

Predictive performance ROTEM parameters

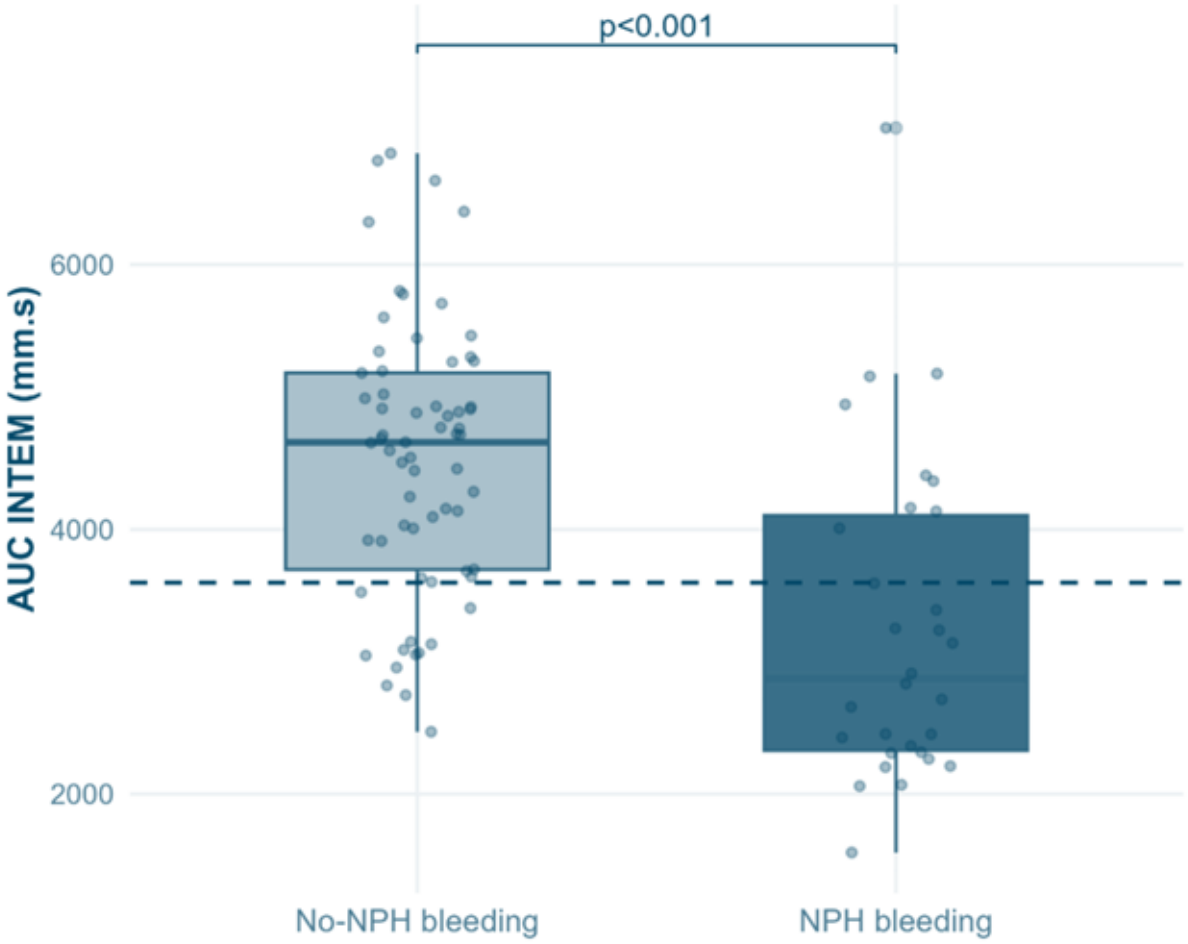
AUC INTEM outperforms individual ROTEM parameters

Parameter	AUROC (95% CI)
AUC INTEM	0.803 (0.697-0.909)
CT INTEM	0.796 (0.707–0.907)
CFT INTEM	0.795 (0.699–0.911)
MCF INTEM	0.788 (0.677–0.898)

Parameter	AUROC (95% CI)
AUC EXTEM	0.787 (0.678-0.896)
CT EXTEM	0.781 (0.669–0.898)
CFT EXTEM	0.775 (0.667–0.883)
MCF EXTEM	0.779 (0.678–0.895)



AUC INTEM best performance



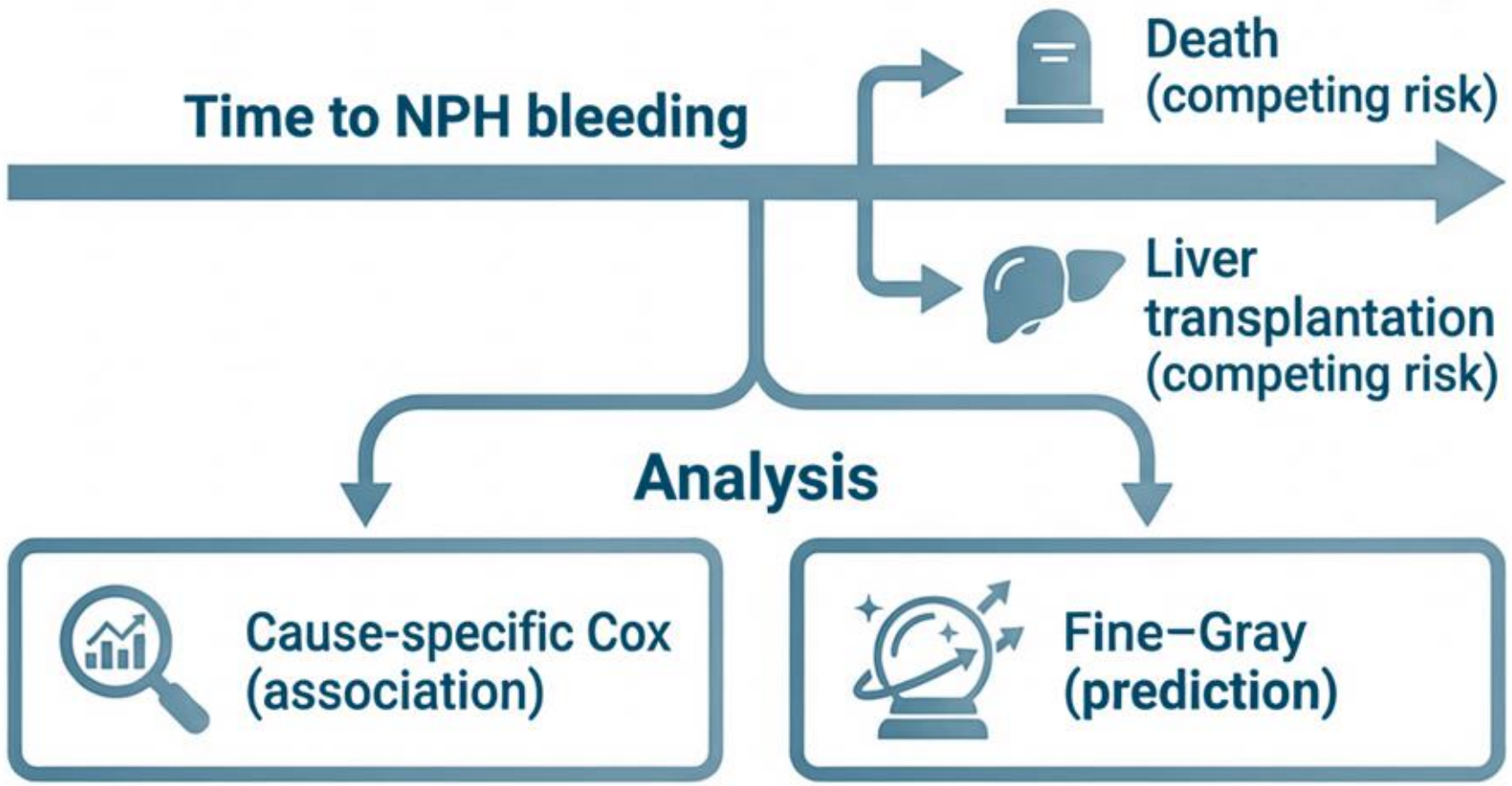
Youden-derived cut-off

- AUC INTEM: **3597**

Performance

- Sensitivity: 70%
- Specificity: 81.5%
- Used for analytical purposes

Time-to-event framework



Univariable time-to-event analysis

Predictor	Cox HR (95% CI)	Fine-Gray sHR (95% CI)	p-value (FG)
AUC INTEM ≤ 3597	**10.29 (4.13–25.62)**	**9.94 (4.17–23.68)**	**<0.001**
ACLF grade 2 vs 1	0.70 (0.21–2.39)	0.69 (0.20–2.35)	0.55
ACLF grade 3 vs 1	**2.62 (1.08–6.34)**	**2.52 (1.13–5.60)**	**0.02**
Bacterial infection	0.86 (0.40–1.85)	0.86 (0.41–1.80)	0.68
Acute kidney injury	1.83 (0.85–3.95)	1.82 (0.87–3.83)	0.07
MELD	**1.71 (1.17–2.49)**	**1.68 (1.23–2.29)**	**0.001**
Fibrinogen level	**0.43 (0.24–0.76)**	**0.44 (0.22–0.89)**	**0.02**
Platelet count	**0.22 (0.10–0.48)**	**0.23 (0.11–0.47)**	**<0.001**

Multivariable time-to-event analysis: baseline model

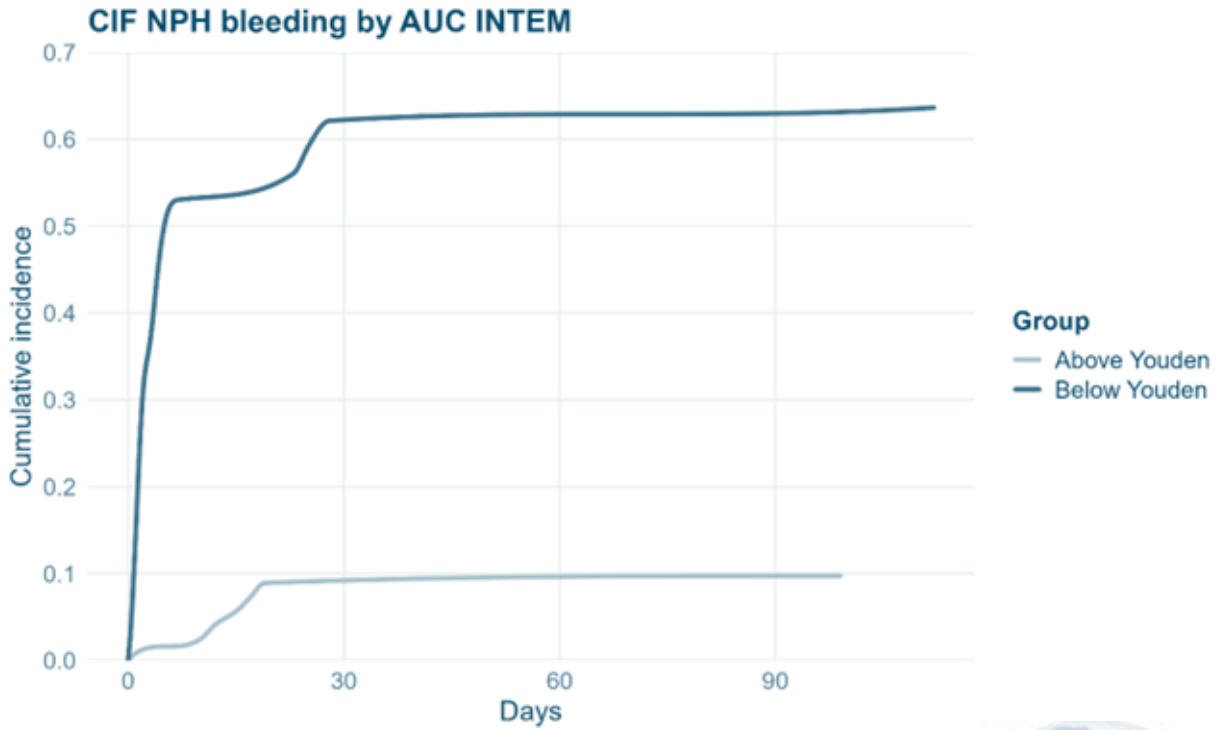
Predictor	Cox HR (95% CI)	Fine–Gray sHR (95% CI)	p-value (FG)
ACLF 3 vs 1	1.11 (0.33–2.50)	0.67 (0.23–1.95)	0.47
Bacterial infection	0.85 (0.48–1.45)	0.79 (0.37–1.68)	0.55
Acute kidney injury	1.62 (0.82–3.01)	1.69 (0.81–3.56)	0.16
MELD	**1.39 (1.04–2.37)**	**1.80 (1.04–3.14)**	**0.04**
Fibrinogen level	0.65 (0.34–0.99)	0.58 (0.27–1.25)	0.17
Platelet count	**0.51 (0.27–0.79)**	**0.33 (0.17–0.66)**	**0.002**

Multivariable time-to-event analysis: model + AUC INTEM

Predictor	Cox HR (95% CI)	Fine–Gray sHR (95% CI)	p-value (FG)
AUC INTEM ≤ 3597	**3.62 (2.06–9.12)**	**5.78 (1.79–18.71)**	**0.003**
ACLF 3 vs 1	0.94 (0.38–1.76)	0.48 (0.17–1.34)	0.16
Bacterial infection	1.02 (0.59–1.86)	1.04 (0.47–2.29)	0.92
Acute kidney injury	1.48 (0.84–3.02)	1.53 (0.68–3.44)	0.30
MELD	**1.31 (1.03–2.23)**	1.84 (0.99–3.40)	0.05
Fibrinogen level	0.82 (0.47–1.24)	0.82 (0.37–1.82)	0.63
Platelet count	**0.73 (0.46–0.96)**	0.65 (0.31–1.41)	0.28

AUC(t) and cumulative incidence

Time	Baseline model AUC(t)	+ AUC INTEM AUC (t)
7 days	0.63	0.80
14 days	0.69	0.78
30 days	0.63	0.80

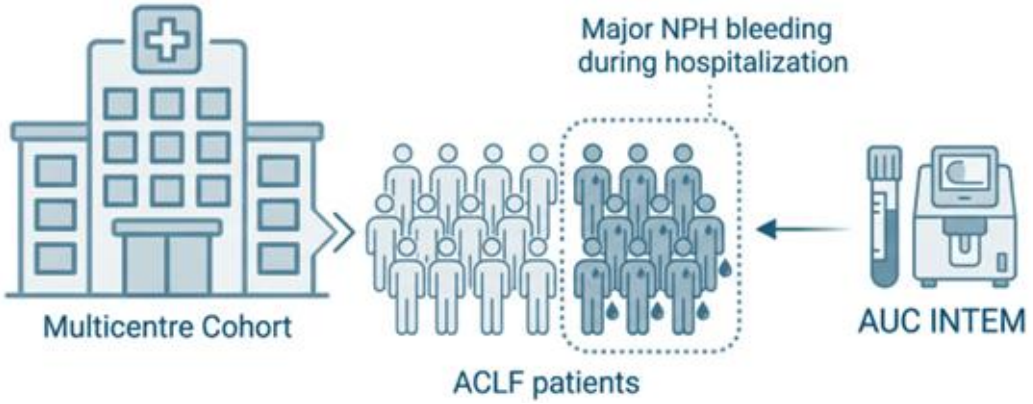


Limitations

- **Retrospective analysis of prospective cohorts**
- **Although well-characterized ACLF-patients with outcomes, sample size remains limited (n=95)**
  - Risk of overfitting despite ridge penalisation and bootstrapping of CIs
- **Internal validation**
  - No external validation cohort
- **AUC not directly available in ROTEM software**
  - Requires mathematical derivation
- **Single time-point measurement**
  - No assessment of dynamic changes in haemostasis

Conclusion

- **NPH-bleeding** frequent complication in ACLF
- Low **AUC INTEM at admission** → **independently associated** with major **NPH-bleeding**
- Improves potentially short-term NPH-bleeding risk prediction beyond clinical and laboratory variables
- Future:
  - Prospective external validation
  - AUC changes over disease course
  - Potential impact of targeted interventions



Thank you very much for your attention

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