

Cirrhosis severity correlates with reduced fibrin generation and enhanced fibrinolysis

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INTRODUCTION	METHODS
- Patients with liver cirrhosis exhibit complex alterations to their haemostatic system, affecting primary haemostasis, coagulation, and fibrinolysis, which could cause severe bleeding and thrombosis. - Standard coagulation studies do not adequately reflect the bleeding or thrombotic risks of patients with cirrhosis. - Global coagulation assays (GCAs) may provide a more comprehensive assessment of haemostasis. However, the impact of liver cirrhosis remains to be fully characterised This study aimed to evaluate the relationship between thrombin and fibrin generation and the thrombosis or bleeding outcomes in patients with cirrhosis.	- Adult patients with liver cirrhosis from <i>Liver @ home Program</i> were recruited. Cirrhosis severity was determined by the Model for End-Stage Liver Disease with sodium (MELD 3.0) score. - Excess citrate plasma were collected for GCAs after routine laboratory testing, including overall haemostatic potential (OHP) assays, calibrated automated thrombogram thrombin generation (CAT-TG) and plasmin generation (CAT-PG) (Figure 1). - GCAs results were compared against age and sex-matched normal controls that collected previously. - Statistical analysis was performed using SPSS version 27.0.1.0 (Chicago, IL, USA).

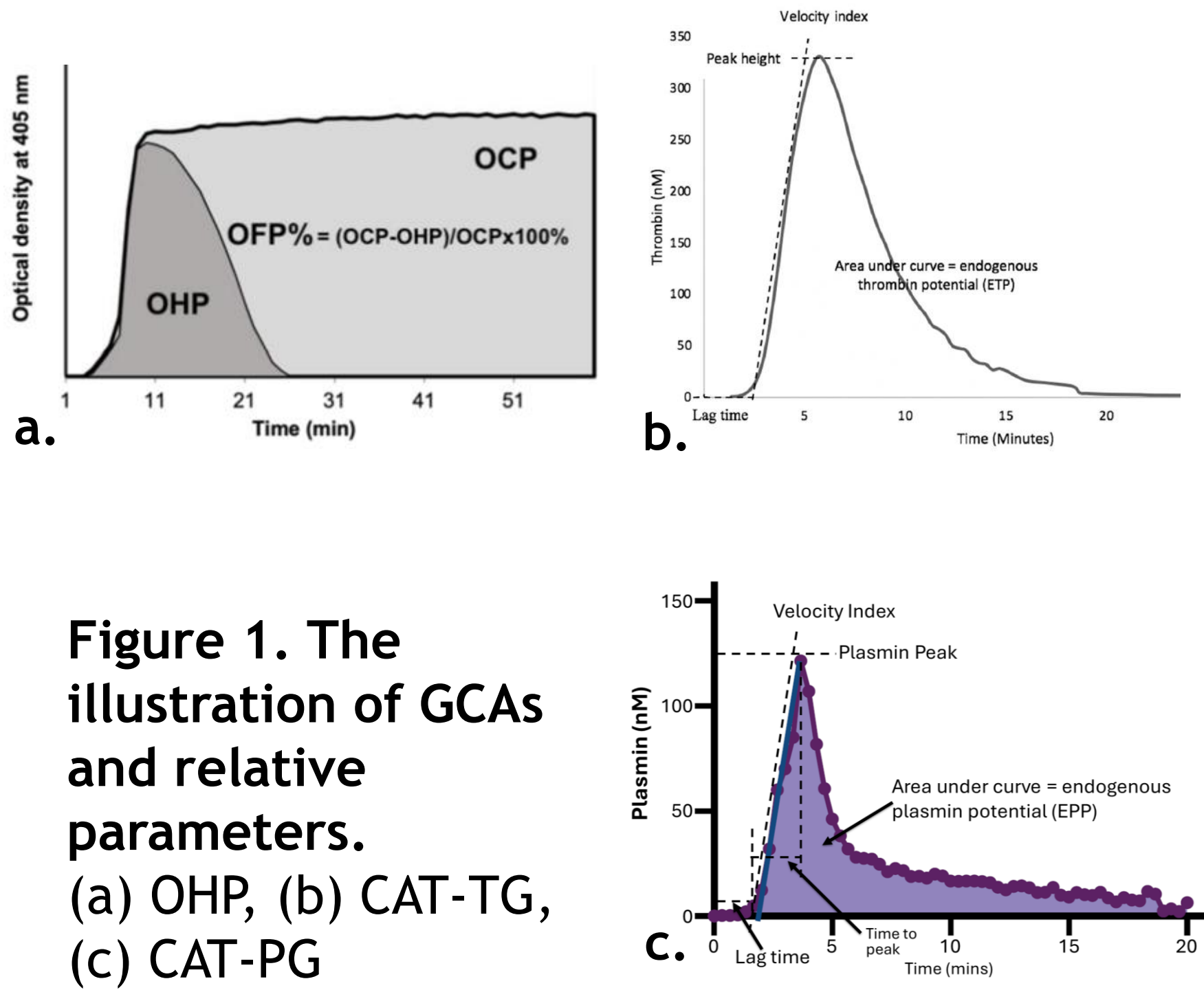
RESULTS	
A total of 55 patients with liver cirrhosis were included and divided into 3 groups based on the MELD scores and estimated 90-day mortality (%) (Table 1). Patients with intermediate and high MELD scores were comparable in GCAs and therefore were combined when compared with normal controls. Low MED patients showed increased thrombin and plasmin generation When compared with normal controls, patients with low MELD demonstrated significantly higher ETP, CAT-TG velocity index, EPP and plasmin peak, indicating an accelerated thrombin and plasmin generation profile. In contrast, no statistical difference was found in OHP parameters between groups (Tale 2, Figure 2). Inter-/High MELD patients showed decreased fibrin & plasmin generation, and increased fibrinolytic capacity When compared with normal controls, patients with Inter-/High MELD presented comparable thrombin generation. In OHP, patients showed significantly reduced in OCP, OHP, and higher OFP, indicating decreasing fibrin generation, but increasing fibrinolysis. In CAT-PG, patients showed significantly decrease in EPP, plasmin peak, and CAT-PG velocity index, demonstrating a flatten plasmin generation profile (Tale 2, Figure 2).	 Figure 1. The illustration of GCAs and relative parameters. (a) OHP, (b) CAT-TG, (c) CAT-PG

Table 1. Patient and normal control demographics and comparisons of GCAs

	Normal control	Liver cirrhosis	MELD 3.0		
			Low (<10)	Intermediate (10~18)	High (>18)
Number	55	55	24	25	6
Female sex, n (%)	18 (32.7%)	18 (32.7%)	7 (29.2%)	10 (40.0%)	1 (16.7%)
Age (years)	58.00	58.0	60.5	58.0	51.0
MELD scores	11.00	N/A	7	14	24
Estimated 90-day mortality (%)			< 0.9%	0.9% ~ 3.7%	>3.7%

Table 2. Comparisons of GCAs between normal and patient groups

	Normal control	Low MELD	P-values (vs normal)	Inter- & High- MELD	P-values (vs normal)
Routine laboratory results					
INR (Ref: 0.80 - 1.20)	1.00	1.00	0.002	1.40	<0.001
PT (Ref: 11.0 - 17.0)	11.00	14.00	<0.001	19.00	<0.001
APTT (Ref: 25.0 - 38.0)	28.84	33.67	<0.001	39.76	<0.001
Fibrinogen (Ref:2.00 - 4.00)	3.01	3.93	<0.001	2.86	0.465
Calibrated automated thrombogram thrombin generation (CAT-TG)					
Endogenous thrombin potential (ETP) (nM·min)	1279	1568	0.001	1485	0.117
Thrombin Peak	205	261	<0.001	239	0.642
TG Velocity Index	52.00	87.85	<0.001	93.14	0.002
Calibrated automated thrombogram plasmin generation (CAT-PG)					
Endogenous plasmin potential (EPP) (nM·min)	243	306	0.013	193	0.005
Plasmin Peak (nM)	42.78	49.56	0.009	36.59	0.004
CAT-PG Velocity index (nM/min)	20.30	21.14	0.362	16.46	0.001
Overall haemostatic potential (OHP) assays					
Overall Coagulation potential (OCP) (units)	35.26	41.93	0.052	26.89	0.008
Overall hemostatic potential (OHP) (units)	6.56	7.21	0.813	3.54	<0.001
Overall fibrinolytic potential (OFP) (%)	79.38	82.36	0.097	84.63	<0.001

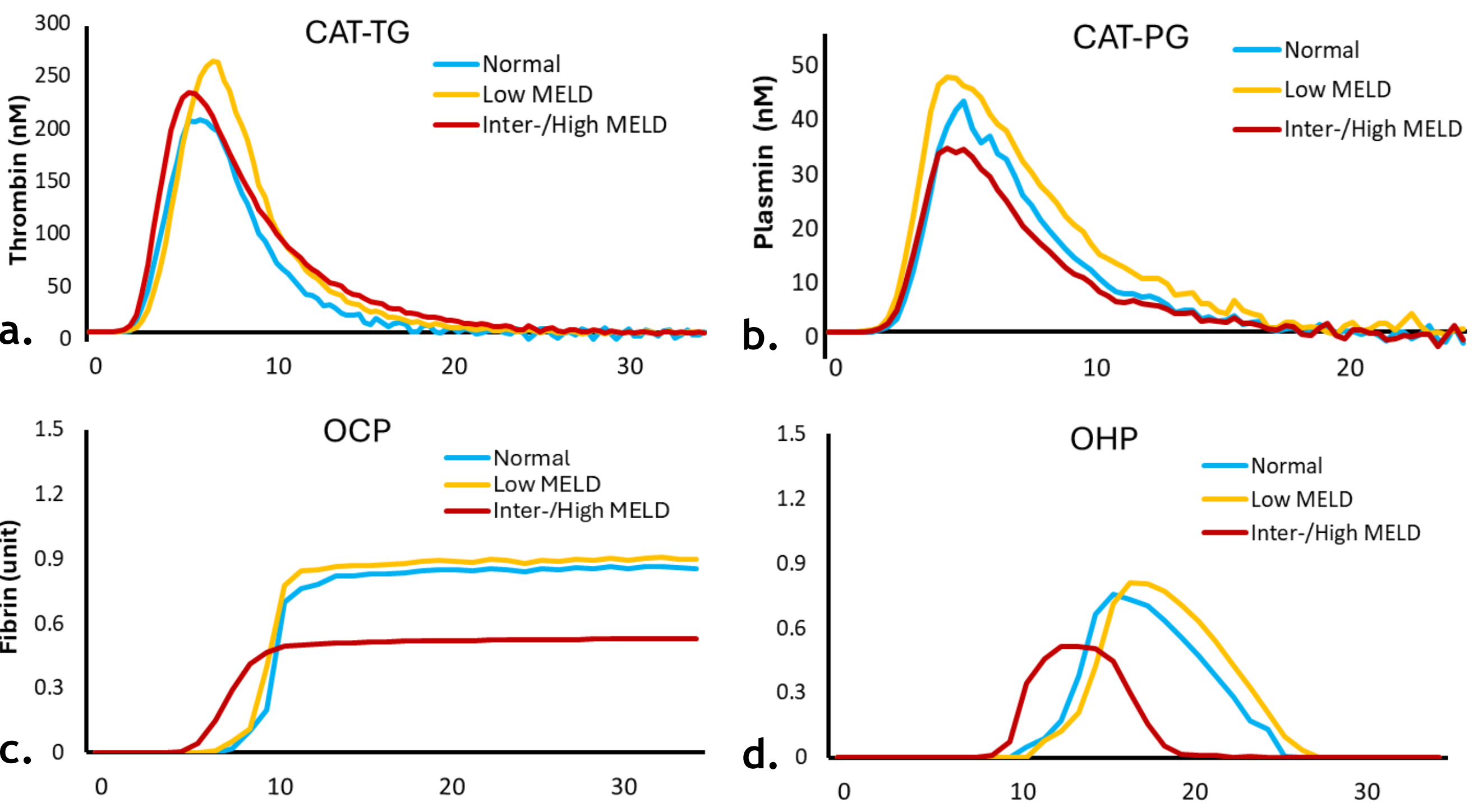


Figure 2. The representative GCA curves of normal controls and patients with low, intermediate and high MELD scores. (a) CAT-TG; (b) CAT-PG; (c) Overall coagulation potential (OCP) in OHP; (D) OHP.

CONCLUSIONS

- Global coagulation assays may better reflect true bleeding and thrombosis risks in liver cirrhosis.
- Compared to normal controls, MELD low-risk cirrhosis patients and intermediate / high risk cirrhosis patients demonstrated differing GCA profiles and may be related to adequacy of compensation.
- Future directions:
 - Correlate GCA findings with clinical bleeding and thrombosis outcomes
 - Develop GCAs as predictive tools for bleeding and thrombosis risk in cirrhosis
 - Help guide blood product usage in cirrhosis, especially perioperative settings