

The crosslinked type III collagen biomarker, CTX-III, reflects fibrosis resolution and is related to intervention and survival in chronic liver disease

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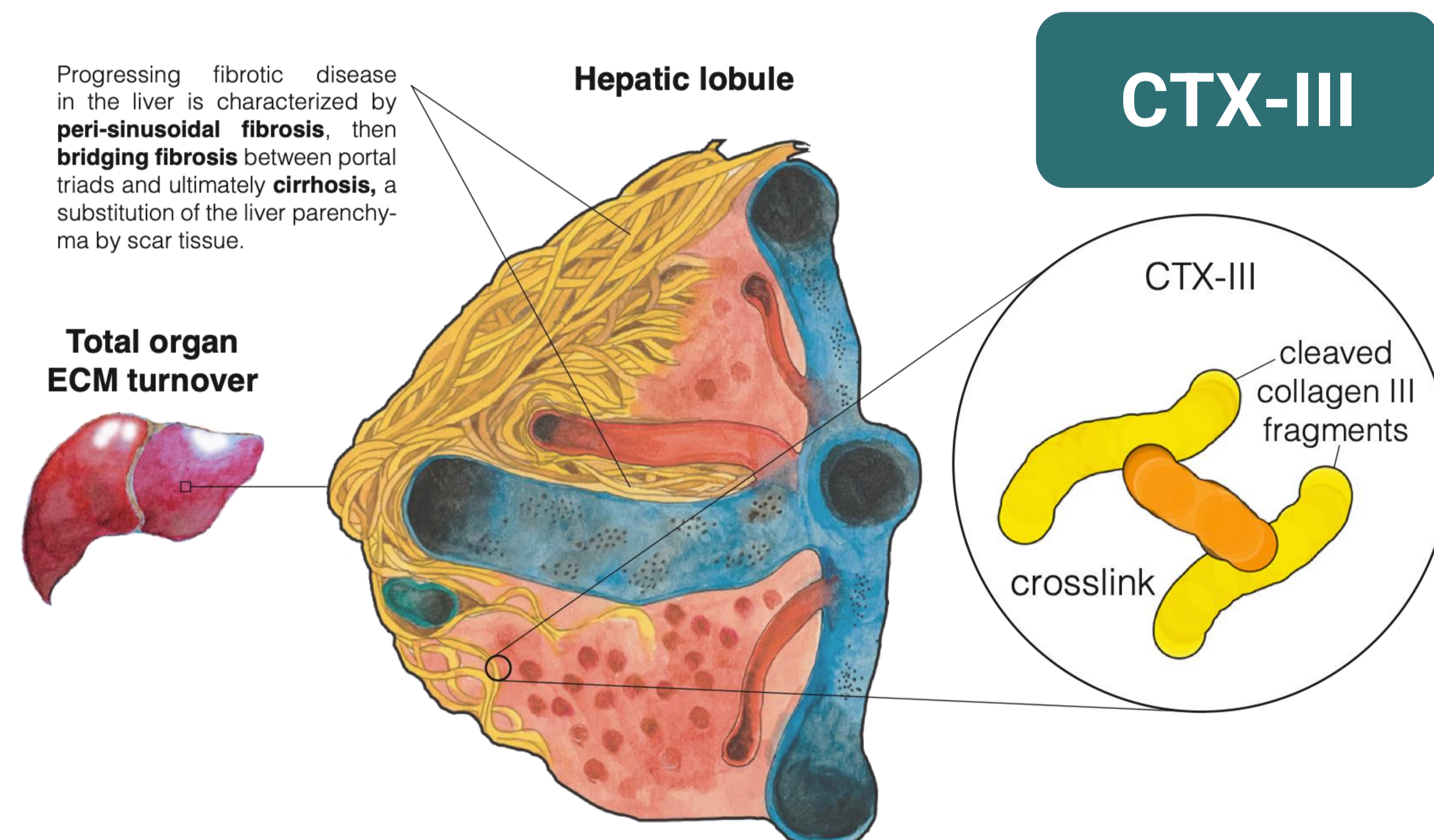
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Background

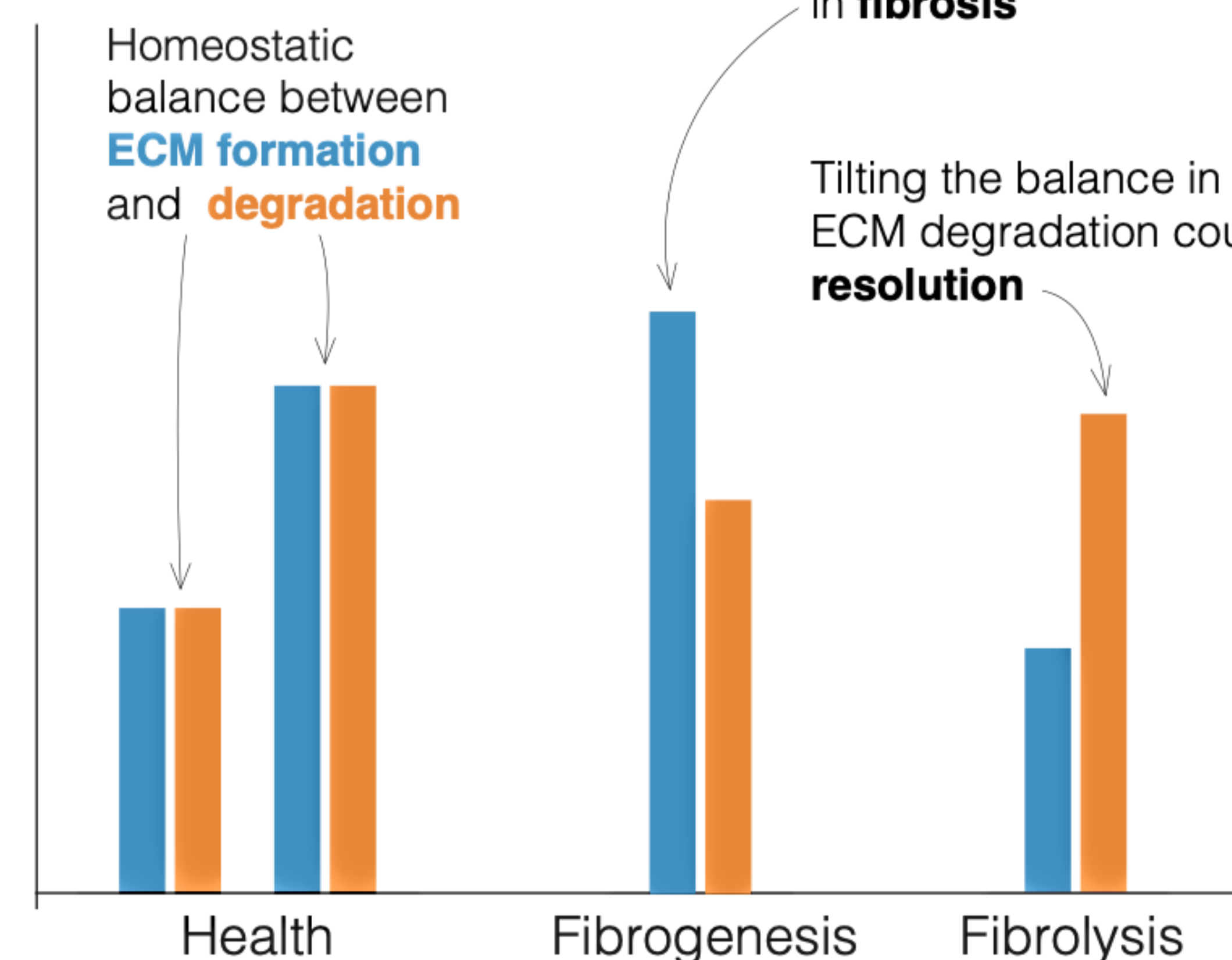
- Liver fibrosis progresses by depositing increasing amounts of crosslinked collagens in the extracellular matrix (ECM), destroying the liver parenchyma in the process. Treatments that hamper fibrosis could trigger the degradation of crosslinked fragments. A biomarker that measures the destruction of crosslinked collagen could open a window into the evolution of disease and the effectivity of therapy.

We hypothesize that circulating fragments of crosslinked collagen type III (CTX-III) can be detected and measured to reflect fibrinolysis, and thus biomark fibrosis resolution.



During disease, both formation and degradation are elevated, but an unbalance towards formation will eventually result in **fibrosis**

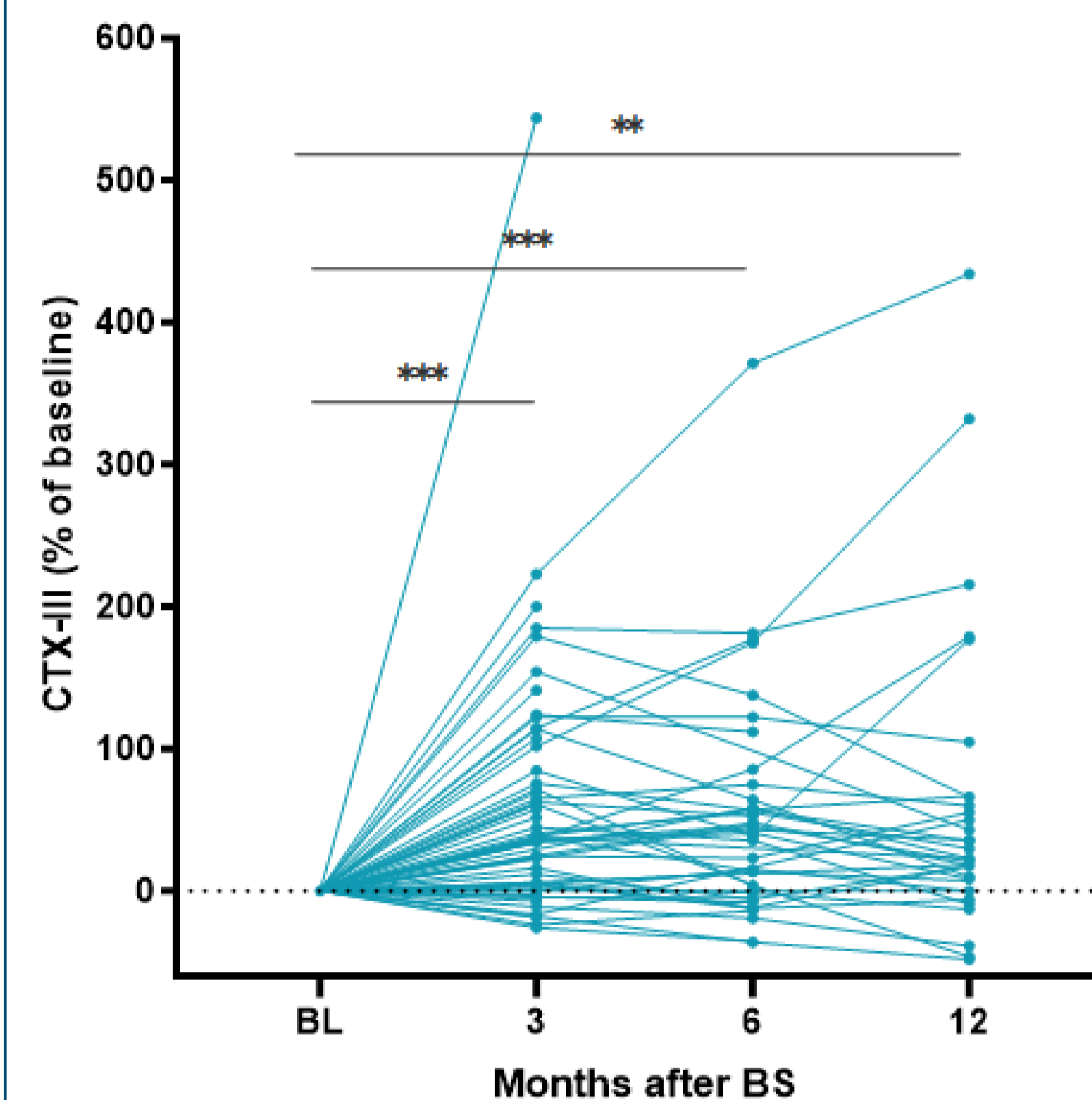
Tilting the balance in favor of ECM degradation could signal **resolution**



Results

CTX-III detects fibrinolysis after surgery

CTX-III increases after bariatric surgery



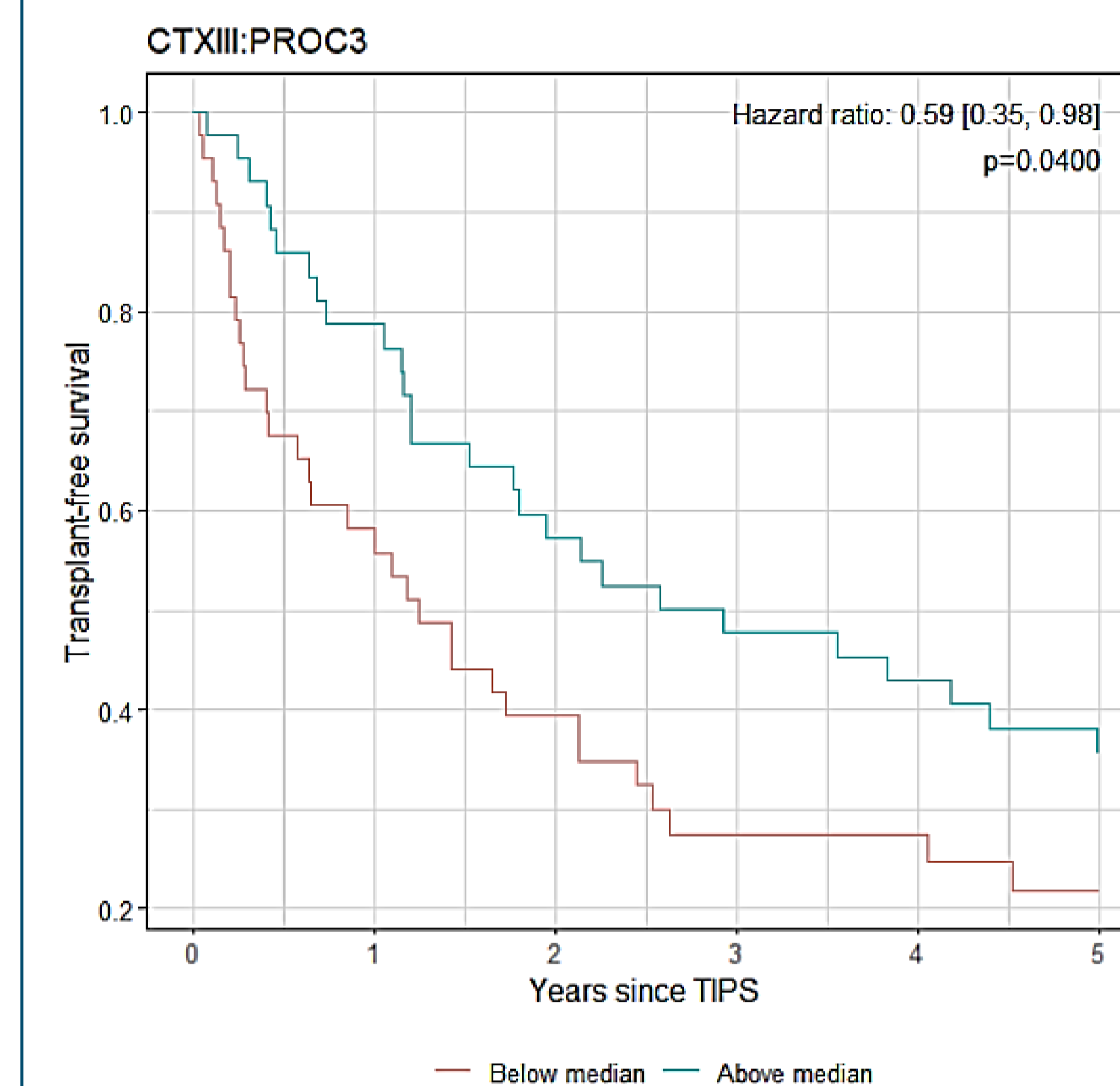
CTX-III increases after bariatric surgery. Interestingly, **CTX-III** levels remain high 1 year after surgery, suggesting the presence of a sustained response to treatment.

CTX-III increase points to a wave of crosslinked collagen type III degradation (fibrinolysis). As overweight patients develop liver and adipose fibrosis, **CTX-III** suggests clinical improvement.

Bariatric surgery patients

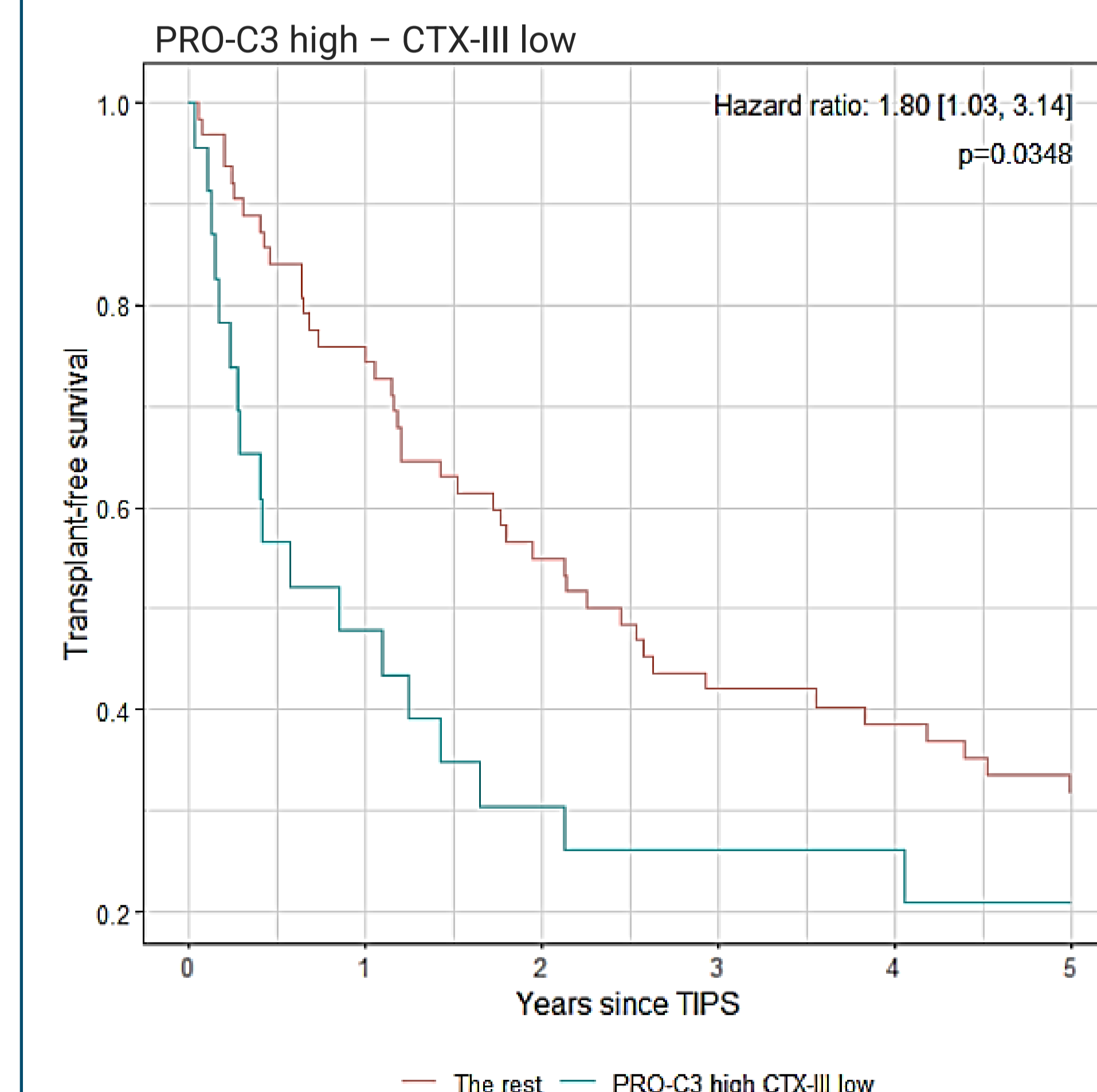
	Baseline (n=65)	Baseline for biopsy (n=33)	Follow-up (n=33)	P-value (n=33)
BMI, kg/m ²	41.9 (37.5-46.1)	41.9 (37.5-44.8)	31.4 (27.8-34.5)	<0.001
Age, years	44 (39-52)	44 (39-52)	44 (39-52)	NA
Sex, female	40 (62%)	18 (55%)	18 (55%)	NA
Type 2 diabetes	16 (24.6%)	8 (24%)	4 (12%)	0.339
AST, U/L	23.5 (20.0-29.0)	23.0 (18.5-30.0)	24.5 (21.8-27.3)	0.922
ALT, U/L	29.0 (23.0-39.0)	31.0 (25.0-37.0)	22.0 (17.0-31.0)	0.006
GGT, U/L	26.0 (18.0-39.0)	31.0 (18.5-39.0)	19 (12.0-21.0)	<0.001
CRP mg/L	4.4 (2.1-7.6)	4.2 (2.1-6.9)	0.9 (0.5-1.9)	<0.001
Fasting glucose	6.1 (5.6-6.6)	6.3 (5.7-6.6)	5.4 (5.2-5.6)	<0.001
HbA1c mmol/mol	37.0 (34.0-38.0)	36.5 (33.8-38.0)	33.5 (32.0-36.3)	0.001
Fibrosis 0/1/2/3/4	2/55/8/0/0	1/28/4/0/0	4/28/1/0/0	0.195
Steatosis 0/1/2/3, n	34/21/9/0	18/11/4/0	30/3/0/0	0.003
Ballooning 0/1/2, n	2/39/24	0/22/11	27/5/1	<0.001
Inflammation	6/44/15/0	3/23/7/0	15/18/0/0	<0.001
NAS	0/6/19/16/10/13/1/	0/2/11/10/5/5/0/0/0		<0.001
PRO-C3, ng/ml	8.8 (8.0-10.2)	8.8 (8.0-10.0)	9.2 (7.8-10.4)	0.161
CTX-III, ng/ml	12.2 (4.2-19.4)	12.9 (4.2-18.6)	14.2 (5.5-31.8)	0.001

CTX-III (fibrinolysis) and PRO-C3 (fibrogenesis) reveal different survival after TIPS



PRO-C3 is a marker of fibrogenesis (progressing fibrosis). By combining it with **CTX-III**, we identified a group of patients with decompensated cirrhosis treated with Transjugular Intrahepatic Porto-systemic Shunt (TIPS) to improve portal hypertension who had a high **CTX-III** to **PRO-C3** and a significantly longer survival after treatment.

Conversely, patients with high **PRO-C3** and low **CTX-III** have a shorter survival. These results suggest that an ECM equilibrium tending to fibrinolysis is correlated to significantly longer life, even in patients with decompensated cirrhosis.



TIPS patients

Sex	
Female	33 (38%)
Male	53 (62%)
Age	
Median (Q1, Q3)	59.0 (52.2, 65.0)
CHILD-PUGH Score	
A	15 (17%)
B	54 (63%)
C	17 (20%)
Deaths or liver transplants within 5yrs	
n(%)	60 (70%)
Deaths with 5yrs	
n(%)	55 (64%)
Liver transplants with 5yrs	
n(%)	5 (6%)
Follow up time (yrs)	
Median (Q1, Q3)	1.8 (0.6, 5.0)
PRO-C3 Baseline (ng/ml)	
Median (Q1, Q3)	29.9 (18.8, 46.3)
CTX-III Baseline (ng/ml)	
Median (Q1, Q3)	2.5 (2.0, 4.0)
CTX-III:PRO-C3	
Median (Q1, Q3)	9.3 (5.0, 20.8)

Conclusions

- CTX-III** is a biomarker engineered to detect enzymatically degraded **crosslinked collagen type III**.
- CTX-III** levels increase after bariatric surgery, suggesting it is possible to measure systemic response to surgical intervention.
- CTX-III:PRO-C3** ratio detects a subpopulation of cirrhotic patients who respond to TIPS with significantly longer survival.