PRO-C4, a biomarker of perisinusoidal fibrosis, is related to cardiometabolic risk factors, steatosis, and liver stiffness

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BACKGROUND

- Early intervention in patients with steatotic liver disease (SLD) is crucial to mitigating the risk of adverse outcomes.
- A histological characteristic of early liver damage is the formation of perisinusoidal fibrosis with thickening of the hepatocyte basement membrane.
- Type IV collagen is a key component of the basement membrane of the extracellular matrix and can be assessed serologically by the biomarker PRO-C4.
- Thus, PRO-C4 could potentially reflect early features of liver damage in patients with early-stage SLD.

Our aim was to explore whether basement membrane remodelling assessed systemically was related to risk factors of chronic liver disease including Met S, liver steatosis assessed by CAP and liver stiffness by Fibroscan.

METHODS

- NordicPRO-C4 was measured in serum samples from a large Danish screening cohort of healthy individuals with known risk factors of SLD (n=4726).

- NordicPRO-C4 was quantified using a chemiluminescence immunoassay on a high sensitivity IDS-i10 automated platform and compared between risk groups and to liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by vibration-controlled transient elastography (VCTE) within well-defined risk groups.

- Patients were divided into risk groups based on known risk-factors of steatotic liver disease. Overall, patients had to be more than 40 years old to be considered "at-risk".
  - Metabolic-related risk group: Patients with either diabetes or a BMI≥30 with presence of the metabolic syndrome.
  - Alcohol-related risk group: Patients consuming more than 14 or 20 units of alcohol weekly for the previous three months for females and males, respectively. In addition, patients with former alcohol overuse and abstinent for less than one year.
  - Both risk factors: Patients with both metabolic- and alcohol-related risk factors

RESULTS

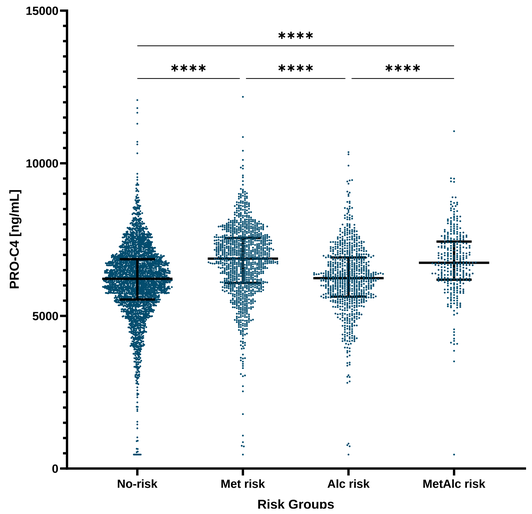
Demographics

Table 1.

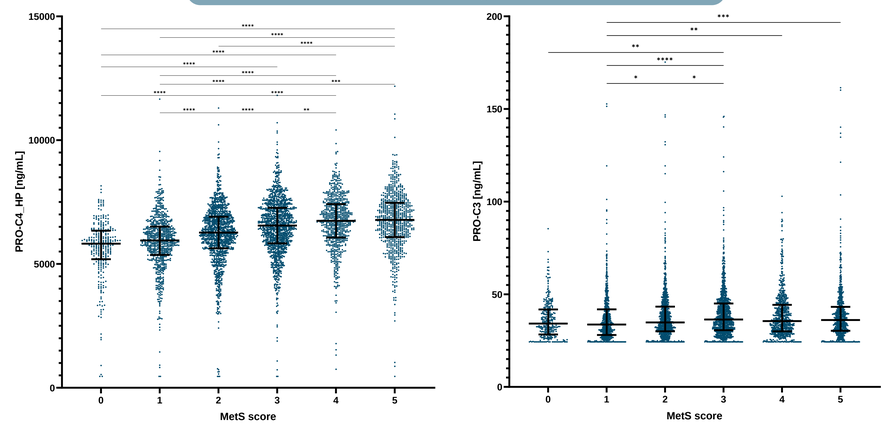
Baseline Characteristics	All patients N = 4726[1]	No Risk N = 2520[1]	Metabolic-related risks N = 1108[1]	Alcohol-related risks N = 782[1]	Both risk factors N = 316[1]	p-value[2]
Gender, male	2311 (49%)	1070 (43%)	521 (47%)	485 (62%)	235 (74%)	**<0.001**
Age, years	57 (±9)	56 (±9)	57 (±8)	59 (±9)	60 (±8)	**<0.001**
BMI, kg/m2	28.5 (±5.7)	26.5 (±4.6)	34.1 (±5.0)	25.5 (±3.3)	33.0 (±4.3)	**<0.001**
MetS grade 0/1/2/3/4/5	283/712/1118/ 1156/672/714	239/573/862/ 463/214/126	0/2/9/ 399/297/397	44/137/245 /186/80/70	0/1/2/ 108/81/121	**<0.001**
Liver Stiffness Measurements (LSM), KpA	4.4 (3.7, 5.4)	4.2 (3.5, 5.0)	5.0 (4.1, 6.0)	4.4 (3.6, 5.2)	5.5 (4.5, 7.6)	**<0.001**
CAP score, dB/m	368 (229, 311)	251 (217, 287)	314 (276, 351)	258 (226, 296)	312 (275, 348)	**<0.001**
PRO-C4, ng/mL	6346 (5722, 7106)	6218 (5539, 6862)	6877 (6082, 7553)	6238 (5635, 6914)	6740 (6188, 7426)	**<0.001**
PRO-C3, ng/mL	35.2 (29.8, 43.3)	34.4 (29.2, 42.0)	35.6 (30.0, 43.9)	36.4 (30.5, 44.8)	39.2 (32.7, 48.6)	**<0.001**

[1]n (%); Median (IQR); Mean (±SD), [2]One-way ANOVA; Kruskal-Wallis test.

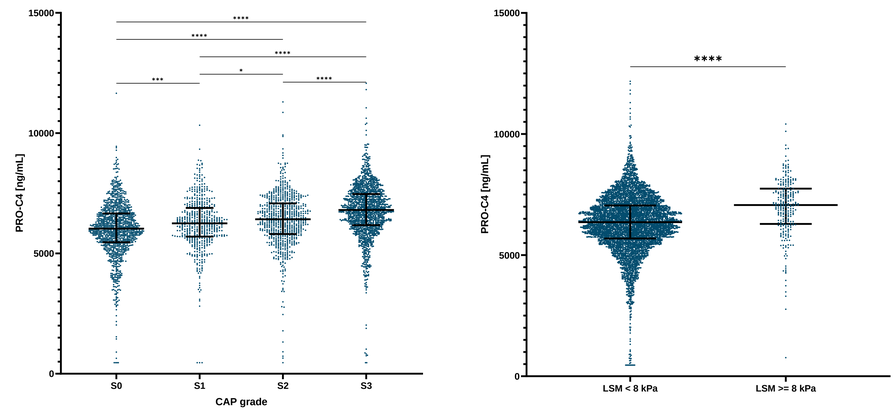
Risk Groups



Metabolic syndrome

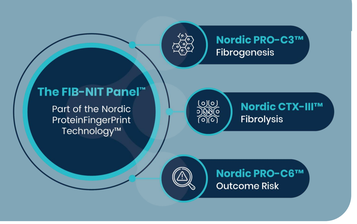


CAP score and LSM by VCTE



CONCLUSIONS

- **Elevated PRO-C4 is associated with presence of cardiometabolic risk factors and LSM>8kpa.**
- **PRO-C4 potentially reflects perisinusoidal fibrosis from early liver damage and repair due to its relation to increasing degree of steatosis.**
- **Interestingly, PRO-C4 was also related to elevated liver stiffness in a population at risk of SLD.**



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