Identification of serum protein signature for primary sclerosing cholangitis and enhanced liver fibrosis score

T. Snir[1], R. Greenman[1], A. Katav[1], R. Aricha[1], M. Frankel[1], J. Lawler[1], F. Saffioti[2], D. Thorburn[3], M. Pinzani[4], I. Vaknin[1], A. Mor[1]

[1] Chemomab, Tel Aviv, Israel ;[2] UCL Institute for Liver and Digestive Health, London, United Kingdom ;[3] The Sheila Sherlock Liver Centre, London, United Kingdom; [4] University College London, London, United Kingdom

Contact information
Ilan.vaknin@chemomab.com

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Introduction

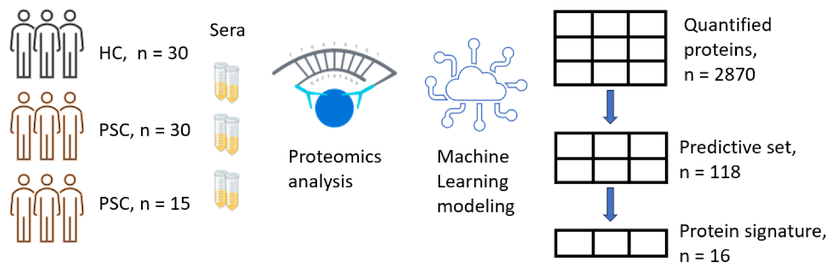
Primary sclerosing cholangitis (PSC) is a rare, progressive disease with no effective treatment and reliable prognostic biomarkers. CCL24, a chemokine with a fibro-inflammatory activity is overexpressed in damaged bile ducts. CCL24 blockade with the neutralizing antibody CM-101 was shown to be safe and active in early clinical trials and is currently being evaluated in a PSC phase 2 clinical study.

Aim

We present a machine learning analysis of serum proteins and clinical stages of PSC, aimed to highlight proteins associated with the disease, including exploration of serum CCL24 levels as a potential predictor of PSC-related complications, such as cirrhosis.

Method

Sera from 30 healthy controls (HC) and 45 patients with PSC were profiled with Olink PEA, quantifying the expression of 2870 proteins and used to train an elastic net model



Proteomic profiling combined with machine learning methods leads to a unique protein signature; a data acquisition process, serum is taken from 3 cohorts of individuals, quantified with proximity-elongation assay (PEA) and used to model disease presence while considering ELF scores and other clinical metrics.

Results

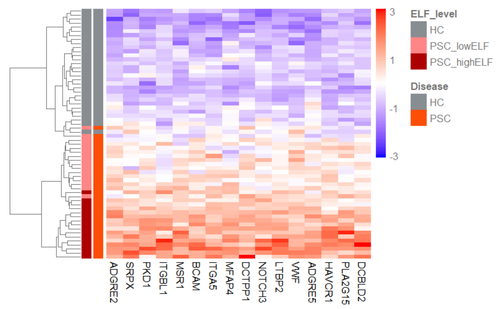
Machine learning successfully predicted the presence of PSC, focusing on a 16- protein signature for disease severity. Further, CCL24 was linked to cirrhosis in patients with PSC

Characteristic	N	Cohort: HC, N = 30[1]	PSC, cohort 1, N = 30[1]	PSC, cohort 2, N = 15[1]
ELF level	75			
HC		30 (100%)	0 (0%)	0 (0%)
PSC, ELF<9.8		0 (0%)	8 (27%)	8 (53%)
PSC, ELF>9.8		0 (0%)	12 (40%)	4 (27%)
PSC, ELF NA		0 (0%)	10 (33%)	3 (20%)
Age [Years]	75	24 (21, 28)	46 (32, 65)	37 (30, 53)
Gender	75			
Female		0 (0%)	11 (37%)	8 (53%)
Male		30 (100%)	19 (63%)	7 (47%)
ELF Score	32	NA (NA, NA)	10.03 (9.30, 10.73)	9.41 (8.96, 10.09)
ALP [U/L]	75	74 (58, 87)	235 (150, 398)	282 (259, 460)
AST [U/L]	75	19 (18, 24)	48 (33, 75)	73 (39, 95)
ALT [U/L]	75	17 (13, 23)	64 (45, 153)	98 (42, 207)
Fibroscan [kPa]	43	NA (NA, NA)	10.20 (8.65, 11.60)	8.10 (6.80, 10.70)

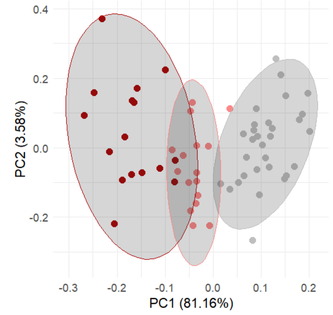
[1]n (%); Median (IQR)

Demographics and baseline characteristics of patients with PSC and healthy controls; Data presented as median (IQR) unless otherwise stated. HC = Healthy controls, ELF = Enhanced Liver Fibrosis

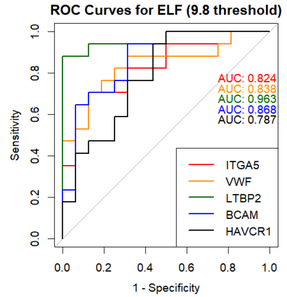
Machine Learning Identifies Key Proteins in Primary Sclerosing Cholangitis Progression



Heatmap of protein signature for PSC and ELF score, showing hierarchical clustering of HC, patients with PSC with low (<9.8) and high (>9.8) ELF scores.

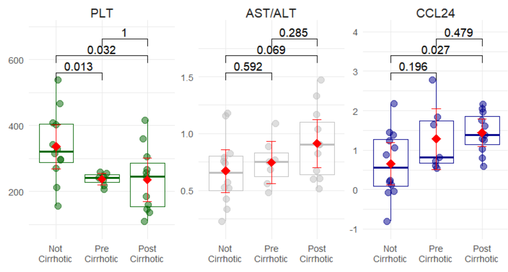


Association of the computational model to disease severity; PCA limited to 16 proteins shows separation for disease presence and severity, stratified by ELF score threshold of 9.8.

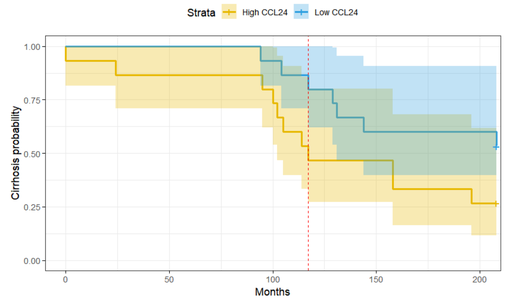


Protein signature for disease severity; ROC curves and area under the curve for the top 5 proteins predicting ELF score with a 9.8 threshold.

High CCL24 is linked to cirrhosis in patients with PSC



CCL24 expression is linked to presence of cirrhosis; Wilcoxon test comparing the mean values of PLT, AST/ALT and CCL24 between PSC patients without cirrhosis, those that developed cirrhosis after serum was taken and patients that were cirrhotic when serum was taken.



CCL24 expression is linked to presence of cirrhosis; Kaplan-Meyer plot stratified by median CCL24 levels showing probability of cirrhosis over time.

Conclusions

Robust proteomic profiling of patients with PSC led to a useful model highlighting a protein signature in disease presence and progression, and CCL24 as linked to cirrhosis. These findings underscore the significance of targeting CCL24 in PSC treatment while the proteomic pattern associated with ELF score may offer promise as a biomarker in the ongoing clinical trial utilizing CM-101—a neutralizing monoclonal antibody targeting CCL24.

References

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