Serum villin-1 level – a tell-tale sign of gut barrier failure in cirrhotic patients with acute decompensation

Dávid Tornai[1], Boglárka Balogh[1], Anikó Csillag[1], András Budai[2], András Kiss[2], Péter Antal-Szalmás[3], Gábor Méhes[4], Lukács Baráth[4], Tamás Tornai[5], István Tornai[1], Zsuzsana Vitális[1], Nóra Sipeki[1], Jonel Trebicka[6,7], Mária Papp[1]

1 Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; 2 Department of Pathology, Forensic and Insurance Medicine, Faculty of Medicine, Semmelweis University, Budapest, Hungary; 3 Department of Laboratory Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; 4 Department of Pathology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; 5 Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; 6 Department of Internal Medicine B, University of Münster, Münster, Germany; 7 European Foundation for Study of Chronic Liver Failure, EF-CLIF, Barcelona, Spain;

INTRODUCTION

- Gut-liver interaction is an important factor in the pathogenesis of liver diseases.
- Insufficient gut barrier function might be the trigger as well as the consequence of acute deterioration of the liver disease (acute decompensation [AD], acute-on-chronic liver failure [ACLF]).
- To date we do not have a clinically useful, non-invasive tool to assess gut barrier function.
- Since multiple organ damage can occur simultaneously in cirrhosis, general damage-associated markers are not suitable for assessing intestinal injury.
- Villin-1 is an actin binding structural protein expressed in brush borders (entire gut, bile canaliculi, proximal tubuli of the kidney).
- Considering the size of the surfaces that express villin-1, we hypothesized that serum villin-1 is largely originates from the gut and it could be used to evaluate gut barrier damage.

PATIENTS AND METHODS

- Patients (n=86) from MICROB-PREDICT has been tested for villin-1 using ELISA
- Clinical data was exported from the study database including medical history, clinical and laboratory results at baseline and follow-up visits.
- Readmissions due to AD or ACLF and mortality have been recorded and used as outcomes.
- 50 healthy controls from the University of Debrecen were also involved

RESULTS

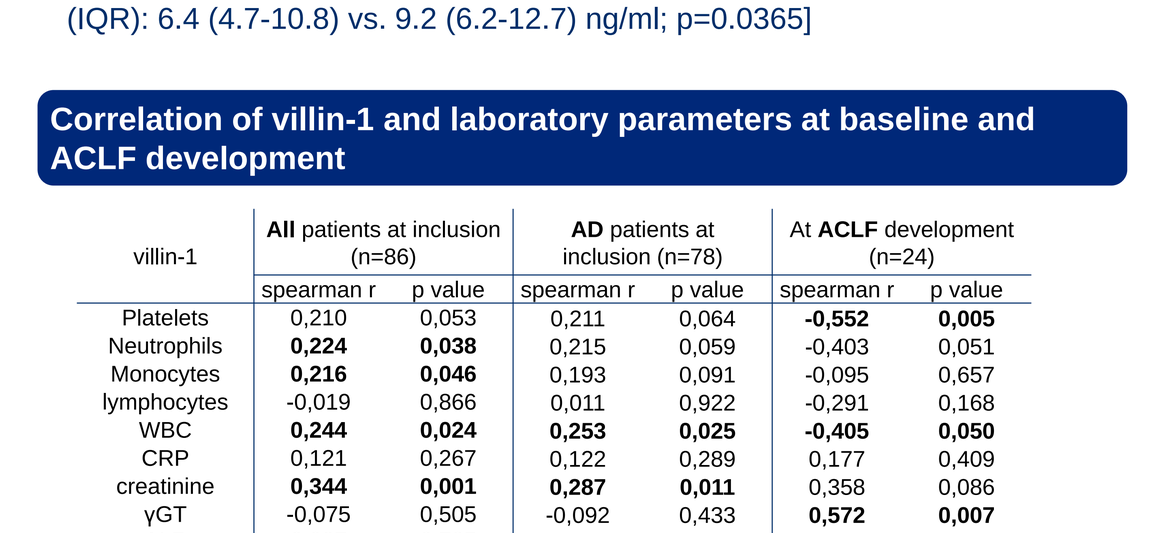
Association of villin-1 with epidemiological and clinical data at baseline

- No association was found between villin-1 levels and:
  - age, sex, etiology, previous AD, Child class, bacterial infection, ascites and HE.
- Lower villin-1 levels were found in patients with alcoholic steatohepatitis [median (IQR): 6.4 (4.7-10.8) vs. 9.2 (6.2-12.7) ng/ml; p=0.0365]

Correlation of villin-1 and laboratory parameters at baseline and ACLF development

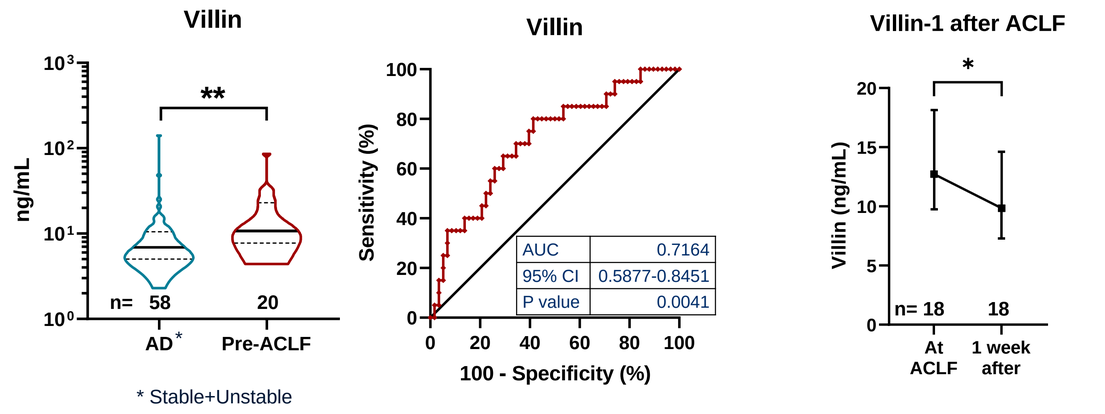
villin-1	**All** patients at inclusion (n=86)		**AD** patients at inclusion (n=78)		At **ACLF** development (n=24)	
	spearman r	p value	spearman r	p value	spearman r	p value
Platelets	0,210	0,053	0,211	0,064	**-0,552**	**0,005**
Neutrophils	**0,224**	**0,038**	0,215	0,059	-0,403	0,051
Monocytes	**0,216**	**0,046**	0,193	0,091	-0,095	0,657
lymphocytes	-0,019	0,866	0,011	0,922	-0,291	0,168
WBC	**0,244**	**0,024**	**0,253**	**0,025**	**-0,405**	**0,050**
CRP	0,121	0,267	0,122	0,289	0,177	0,409
creatinine	**0,344**	**0,001**	**0,287**	**0,011**	0,358	0,086
γGT	-0,075	0,505	-0,092	0,433	**0,572**	**0,007**
ALP	0,037	0,735	0,049	0,670	0,116	0,598
ALT	-0,042	0,700	-0,063	0,581	-0,041	0,853
AST	-0,062	0,570	-0,068	0,557	0,325	0,131
INR	-0,083	0,448	-0,049	0,670	0,061	0,783
bilirubin	-0,099	0,366	-0,075	0,513	0,118	0,583
albumin	0,042	0,700	-0,002	0,990	-0,049	0,823
MELD	0,059	0,591	0,004	0,976	0,208	0,341
Maddrey	-0,095	0,390	-0,052	0,654	-0,024	0,913
GCS	-0,087	0,428	-0,063	0,583	-0,054	0,800
CLIF AD			**0,294**	**0,009**		
CLIF OF	0,094	0,387	0,032	0,778	0,080	0,716
CLIF ACLF					-0,149	0,496

Villin-1 levels in controls and outcome related patient groups

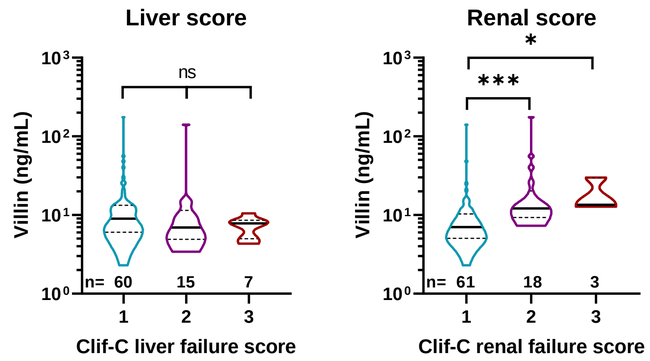


RESULTS (continued)

Serum villin-1 level is increased before ACLF and it decreases after the event



Serum villin-1 levels are associated with CLIF-C renal- but not with liver failure score



Serum villin-1 predicts 90-day mortality independently of renal failure

Supplemented with patients included in the „big" PREDICT cohort from the University of Debrecen

CONCLUSIONS

- Serum villin-1 levels increase parallel with outcome related severity groups. It is significantly higher in patients who are going to develop ACLF compared to patients who are not, and it decreases in survivals after the event.
- Serum villin-1 levels increase parallel with CLIF-C renal but not liver failure score, indicating that renal damage might contribute to increased serum villin-1 levels, but liver damage does not affect villin-1 serum concentrations.
- High serum villin-1 levels can predict 90-day mortality with especially high efficiency in combination with CLIF-C AD score. The 90-day mortality predicting capacity of villin-1 is independent of the present of renal failure suggesting that kidney damage is not the main determinant of villin-1 levels.
- Therefore, the majority of serum villin-1 probably originates from the gut, and it has the potential to increase the accuracy of current risk estimation methods by providing information on gut injury/failure.

Contact: **Maria Papp, MD, PhD, DsC (papp.maria@med.unideb.hu)**
David Tornai, MD, PhD (tornai.david@med.unideb.hu)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694. This reflects only the authors' view and the European Commission is not responsible for any use that may be made of the information it contains.

Follow MICROB-PREDICT on twitter: **www.twitter.com/MicrobPredict**

MICROB-PREDICT online: **www.microb-predict.eu**