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CASS

Non-recognized liver impairment in critically ill patients is frequent and hazardous

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BACKGROUND

The incidence and clinical importance of acute liver impairment in critically ill patients is debated. Hyaluronic acid (HA) is released from connective tissue, hepatically eliminated and has been shown to reflect liver function and prognosis in other populations. The aim of the current study was:

i) to determine how frequent intensive care patients suffer from clinically relevant liver impairment
ii) to determine whether this potential liver impairment has impact on 28-day survival.

METHODS

A 1,200 intensive care patient cohort from a randomized trial (> 80% infected). Patients were excluded if stored serum specimens were too sparse for HA analysis, and if the liver biomarkers bilirubin, INR and Model for End-stage Liver Disease (MELD) were not available at baseline.

All patients with chronic liver disease were excluded. In the final cohort of 839 patients (**figure 1**) all had HA measured in an immunoturbidimetric assay (HA in healthy controls is ~40 ng/mL).

Table 1

Baseline characteristics for critically ill patients according to medical or surgical background

	Medical intensive care patients	Surgical intensive care patients
Median (Inter Quartile Range)		
Age (years)	68 (58 - 76)	68 (59 - 76)
Apache II Score	19 (14 - 26)	18 (13 - 23)
Body Mass Index	24.7 (22.2 - 27.8)	24.8 (22.5 - 27.8)
Estimated Glomerular Filtration Rate (ml/min/1.73 m²)	53.8 (28.2 - 91.1)	45.2 (26.3 - 71.9)
Hyaluronic Acid (ng/mL)	143.1 (66.1 - 437.1)	214.8 (68.6 - 554.0)
INR	1.3 (1.1 – 1.6)	1.4 (1.3 – 1.7)
Bilirubin	8 (5 – 14)	11 (6 – 20)
MELD score	13.5 (9.4 – 20.1)	15.5 (11.7 – 20.9)
Temperature (°Celsius / °Fahrenheit)	37.3 (36.5 – 38.1) / 99.1 (97.7 – 100.6)	37.3 (36.2 – 38.0) / 99.1 (97.2 – 100.4)
Frequencies, n (%)		
Severe sepsis/septic shock	239 (38.8%)	117 (52.5%)
Cancer	62 (10.1%)	30 (13.5%)
Charlsons comorbidity score ≥2 (vs. 0-1)	205 (33.3%)	77 (34.5%)
Gender (Male vs. Female)	317 (51.5%)	123 (55.2%)
Chronic Obstructive Pulmonary Disease (yes vs. no)	158 (25.7%)	26 (11.7%)
Mechanical ventilation (yes vs. no)	413 (67.1%)	157 (70.4%)

Baseline: 0-24 hours after intensive care admission. MELD: Model for End-Stage liver Disease

Figure 1

Flow of patients in the study

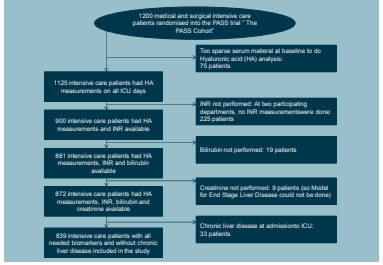


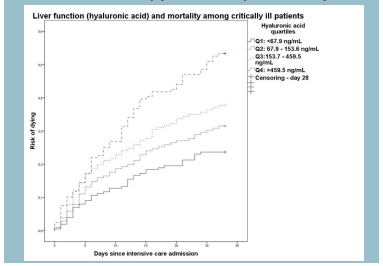
Table 2

Risk of death within 28 days among critically ill patients Multivariable Cox proportional hazards model

	p-value	Hazard ratio	95,0% CI for Hazard ratio	
			Lower	Upper
Age ≥ 65 years (yes vs. no)	<0.0001	1.9	1.4	2.6
Apache II score ≥ 25 (yes vs. no)	0.007	1.5	1.1	1.9
Severe sepsis/Septic shock (vs. milder or no infection)	0.9	1.0	0.8	1.4
Cancer (yes vs. no)	1.0	1.0	0.7	1.6
Charlson comorbidity score ≥ 2 (yes vs. no)	0.02	1.4	1.1	1.9
Surgery prior to intensive care (yes vs. no)	0.03	0.7	0.5	1.0
Body Mass Index ≥ 25 (vs. <25)	1.0	1.0	0.7	1.4
Gender (male vs. female)	0.3	1.1	0.9	1.5
Estimated GFR				
> 60 ml/min/1.73 m², reference	-	-	-	-
30-60 ml/min/1.73 m²	0.3	0.9	0.6	1.2
< 30 ml/min/1.73 m²	0.1	0.8	0.6	1.1
Chronic Obstructive Pulmonary Disease (yes vs. no)	0.1	1.3	0.9	1.7
Mechanical ventilation (yes vs. no)	0.001	1.7	1.2	2.3
Hyaluronic acid quartiles				
1st quartile, reference	-	-	-	-
2nd quartile	0.4	1.2	0.8	1.8
3rd quartile	0.04	1.5	1.0	2.3
4th quartile	0.001	1.9	1.3	2.9

Figure 2

Liver function (hyaluronic acid) and mortality



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RESULTS

Biomarker levels at baseline were (median [IQR]), HA (ng/mL): 153.6 [67.9 – 459.5], INR: 1.3 [1.1 – 1.6], bilirubin (mg/dL): 0.53 [0.29 – 0.88], MELD: 13.9 [9.9 – 20.4]. Significant correlations were present between all liver markers (rho 0.15 – 0.56). The mortality risk corresponded directly to the HA quartile they belonged to. The 28-day mortality was ~55% for patients in the 4th quartile vs. ~22% in 1st quartile, logrank, p<0.0001 (**figure 2**). In a multivariable Cox regression model adjusted for known and suspected predictors of mortality, HA quartile III (HR 1.5 [95% CI: 1.0 – 2.5]) and IV (HR 1.9 [95% CI: 1.3 – 2.9]) were found to be strong independent predictors of mortality in intensive care patients (ref Q1). Substantially higher risk was also found in the upper quartile for bilirubin (HR 1.6 [95%CI: 1.1 – 2.3]).

CONCLUSION

Liver impairment, measured by three liver biomarkers and MELD, was frequent in these critically ill patients and was highly predictive for mortality. It is biologically plausible that patients who suffer from liver impairment in critical illness will also be less likely to be able to react adequately to a severe infection and therefore at a higher risk of dying.
The mechanisms causing this liver impairment should be explored to detect targets for interventions to improve outcome.

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