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Hyaluronan serum concentrations are elevated in critically ill patients and associated with disease severity

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ABSTRACT

Objectives: The matrix protein hyaluronic acid (HA, hyaluronan) has possibly additional immune-regulatory functions in inflammation. We aimed at evaluating serum HA concentrations in critically ill patients.

Design and methods: We analyzed serum HA levels in 164 critically ill patients at a medical ICU and 61 healthy controls, with respect to organ dysfunction, systemic inflammation and mortality.

Results: Hyaluronan serum concentrations upon admission to ICU were significantly elevated in critically ill patients compared to healthy controls, with the highest levels in patients with pre-existing liver cirrhosis or sepsis. HA levels were closely correlated with biomarkers of hepatic and renal function, systemic inflammation, demand of treatment measures and clinical scores of disease severity, but could not predict risk of mortality.

Conclusions: Measurement of serum HA may supplement the assessment of disease severity in ICU patients. Our data suggest that HA might have implications in the pathogenesis of critical illness and sepsis.

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Introduction

Hyaluronic acid (HA), also termed hyaluronan, is a high molecular weight glycosaminoglycan with linear polysaccharide structure and synthesized by many cell types, including fibroblasts or other matrix-producing cells [1]. In healthy individuals, HA is abundantly found in heart valves, skin, skeletal tissues, the vitreous of the eye, and synovial fluid, thus representing a matrix component that exerts lubricant-like functions by binding large amounts of water [2]. More recently, it has been unraveled that HA, besides its properties as a matrix protein, additionally exerts functions in the regulation of inflammatory processes [3]. Interestingly, inflammatory cytokines like tumor necrosis factor (TNF), lymphotoxin and interferons stimulate HA production, for instance after lung injury [4]. The accumulation of HA in inflamed tissue is subsequently involved in attracting neutrophils and T-cells and by modulating their effector functions [5,6].

HA is normally found at low concentrations in the circulation, because it is rapidly cleared from the bloodstream by the endothelial cells in the liver sinusoids [7]. HA serum concentrations have been

evaluated as a biomarker for fibrotic liver diseases. Serum HA levels appear to be closely associated with the degree of fibrosis in patients with chronic liver diseases, due to the increased extracellular matrix deposition in hepatic fibrosis and reduced clearance by sinusoidal endothelial cells [8–10]. Moreover, serum HA levels have been described to be elevated in patients with sepsis, potentially caused by impaired endothelial clearance in the liver sinusoids, but the exact regulation of HA levels remained elusive [11,12]. More recently, experimental animal models suggested that high-molecular weight HA might be a promising new treatment option for sepsis-induced lung injury by ameliorating pulmonary capillary leakage and by limiting inflammatory cascades [13,14].

However, there are no sufficient data at present concerning the mechanisms of HA regulation in critically ill patients from large cohorts. Before testing the possible therapeutic effects of HA in humans, clinical studies on profiles of endogenous HA regulation in the critically ill are needed. Therefore, we conducted the present study on a large cohort of well characterized critically ill patients to provide information about HA serum concentrations in different circumstances of critical disease such as sepsis or decompensated liver cirrhosis, to identify possible pathogenic functions of HA by correlations with a wide number of markers of inflammation, organ dysfunction and metabolism, and to examine potential protective effects of HA for the outcome of critically ill patients.

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Patients and methods

Patients and control collective

The study population consisted of 164 critically ill patients (100 males/64 females, median age 64 years; range 21–90 years) who were admitted to the Medical ICU at the RWTH-University Hospital Aachen, Germany. Patients who were expected to have a short-term (<72 h) intensive care treatment due to post-interventional observation or acute intoxications were not included into this study [15]. 101 patients who met the criteria proposed by the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference Committee for severe sepsis and septic shock were categorized as sepsis patients, the others (n = 63) as non-sepsis patients (Table 1) [16]. Non-sepsis patients were further subdivided into patients with or without systemic inflammatory response syndrome (SIRS) [17]. Pneumonia was identified in the majority of sepsis patients as the disease-determining origin of infection. Non-sepsis patients were admitted to the ICU mainly due to cardiopulmonary diseases (myocardial infarction, pulmonary embolism, and cardiac pulmonary edema) or other critical conditions and did not differ in age or sex from sepsis patients (Table 2). Liver cirrhosis was established as a clinical diagnosis by two independent experienced hepatologists based on patient's history, laboratory values and hepatic imaging (ultrasound, CT, MRI) in 12 patients [18]. The medium length of stay at the ICU was 7 days (range 1 to 70 days). Patient data, clinical information and blood samples were collected prospectively.

The control population consisted of 61 matched blood donors. The healthy volunteers had normal levels of aminotransferases, normal blood counts and negative markers for hepatitis B, hepatitis C and HIV.

The study protocol was approved by the local ethics committee and conducted in accordance with the ethical standards laid down in the Declaration of Helsinki (ethics committee of the University Hospital Aachen, RWTH-University, Aachen, Germany, reference number EK 150/06). Written informed consent was obtained from all participants.

Measurement of HA serum concentrations

Blood samples for HA measurement in patient groups were collected upon admission to the ICU (prior to therapeutic interventions)

Table 1
Baseline patient characteristics and hyaluronan serum concentrations.

Parameter	All patients	Sepsis	Non-sepsis	P-value ^a
Number	164	101	63	–
Sex (male/female)	100/64	60/41	40/23	–
Age median (range)[years]	64 (21–90)	66 (21–90)	61 (21–85)	n.s.
APACHE-II score median (range)	19 (2–43)	22 (4–40)	14.5 (2–43)	<0.001
SOFA score median (range)	8 (0–19)	9 (0–19)	6 (0–17)	0.002
ICU days median (range)	7 (0–70)	9 (0–70)	5 (1–41)	0.001
Death during ICU n(%)	34 (21%)	28 (28%)	6 (10%)	–
Mechanical ventilation n(%)	119 (74%)	79 (80%)	40 (64%)	–
Ventilation time median (range) [h]	179 (0–1846)	210 (0–1846)	93 (0–986)	0.01
Pre-existing liver cirrhosis n(%)	12 (7%)	5 (5%)	7 (11%)	–
Hyaluronic acid day 1 median (range) [µg/L]	270.5 (0–2842)	344 (0–2641)	168 (0–2842)	0.02
Hyaluronic acid day 3 median (range) [µg/L]	252.5 (23–2662)	253 (23–2662)	187 (23–621)	n.s.
Hyaluronic acid day 7 median (range) [µg/L]	192 (23–2625)	212 (23–2468)	163 (62–2625)	n.s.

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; SOFA, sequential organ failure assessment; n.s., not significant.

Day 1 refers to admission at ICU, days 3 and 7 to subsequent time-points during the course of ICU treatment.

^a P-value between sepsis and non-sepsis patients (U-test).

Table 2
Disease etiology of the study population.

		Sepsis n = 101	Non-sepsis n = 63
ICU patients with sepsis			
Site of infection	n (%)		
Pulmonary		57 (56%)	
Non-pulmonary		44 (44%)	
ICU patients without sepsis	n (%)		
Cardiopulmonary disease			19 (30%)
Non-sepsis other			44 (70%)

as well as in the mornings of day 3 and day 7 after admission. After centrifugation at 2000 × g, patient and control serum samples were stored at –80 °C until analysis.

Quantitative determination of serum HA concentrations in the patient and control groups was carried out using an automated latex agglutination assay according to the manufacturer's instructions (WAKO, Osaka, Japan). Serum samples were mixed with recombinant hyaluronic acid binding protein (rHABP) and latex particles coated by anti-HABP monoclonal mouse-antibody. The degree of turbidity in the mixed sample, measured optically using the ThermoFisher KoneLab 30i analyzer (ThermoFisher Scientific, Hudson, New Hampshire, USA), is proportional to the HA concentration in the serum sample. In human serum, the assay was linear within a dilution range from 1:2 to 1:10. Control samples containing defined HA concentrations in human serum could be reliably measured (within a range of 91–110% from the predicted value). Recombinant HA was used to generate a standard calibration curve (range 0–1000 µg/L) [9]. The coefficient of variation for intra-assay was 5.6–7.9% and inter-assay imprecision was 2.0–5.3%, respectively.

Measurement of inflammatory and experimental biomarkers

In addition to HA and routine clinical chemistry markers, the following parameters were determined from stored samples of all patients upon admission to the ICU: cystatin C, TNF-alpha, IL-6 and IL-10 (all Siemens Healthcare, Erlangen, Germany), procalcitonin, NT-proBNP (both Roche, Mannheim, Germany) and soluble urokinase plasminogen activator receptor (suPAR, ViroGates, Birkerød, Denmark) and NT-proCNP (BioMedica, Vienna, Austria; distributor: Immundiagnostik AG, Bensheim, Germany) serum concentrations were measured by commercial nephelometric, chemiluminescence and enzyme immunoassays, following manufacturers' instructions [17,19].

Statistical analysis

Owing to the skewed distribution of most parameters, values are given as median and range. Spearman rank correlations are given in order to quantify the degree of association between two variables, where P-values below 0.05 were considered statistically significant. Comparisons between subgroups are illustrated using box-and-whiskers plots, which display a statistical summary of the median, quartiles, range and extreme values. The whiskers extend from the minimum to the maximum value excluding outside and far out values, which are displayed as separate points. An outside value is defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range. A far out value is defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range [20]. Differences between two groups were assessed by Mann-Whitney-U-test. Receiver operating characteristic (ROC) curve analysis and the derived area under the curve (AUC) statistic provide a

global and standardized appreciation of the accuracy of biomarkers. ROC curves were generated by plotting sensitivity against 1-specificity [19]. To determine which of the markers HA, hepatic function (depicted as pseudocholinesterase and INR), renal function (creatinine) and inflammation (C-reactive protein, white blood cell count) have an impact on the risk for the development of sepsis in the subgroups of non-cirrhotic patients, multiple regression analysis was performed using age and sex as covariates [17].

The prognostic value of HA serum concentrations to predict survival was tested by Kaplan Meier curves and log-rank statistics [20]. All statistical analyses were performed using SPSS version 12.0 (SPSS, Chicago, IL, USA).

Results

Hyaluronan serum concentrations are elevated in critically ill patients with highest values in cirrhosis and sepsis

To unravel the potential pathogenic role or diagnostic value of serum hyaluronic acid (HA) in critically ill patients, we measured HA serum concentrations in 164 patients upon admission to the medical ICU prior to therapeutic interventions. Critically ill patients displayed significantly higher HA serum concentrations as compared with healthy controls (median 270.5 µg/L, range 0–2842, in ICU patients versus 11 µg/L, range 0–195, in controls, $P < 0.001$; Fig. 1A). Hyaluronan serum levels were also measured at days 3 and 7 after admission to the ICU and remained elevated compared with controls (Table 1). In the

subsequent statistical analyses, only the HA values at ICU admission were used.

HA is well validated in patients with different stages of chronic liver diseases as a non-invasive biomarker reflecting the extent of liver fibrosis [8]. We found significantly elevated serum HA levels in ICU patients with pre-existing liver cirrhosis ($n = 12$, median 1014 µg/L, range 132–2842) as compared to non-cirrhotic critically ill patients ($n = 152$, median 244 µg/L, range 0–2838, $P = 0.003$, Fig. 1B). Using the cut-off of 500 µg/L for HA serum concentrations, we found a sensitivity of 66.7% and a specificity of 66.4% for predicting cirrhosis within critically ill patients, while a cut-off of 600 µg/L for HA improved specificity to 71.1%, whereas sensitivity decreased to 58.3%.

HA in ICU patients may not only predict extracellular matrix proteins from the liver or other fibrotic tissues, but could also stem from bacterial wall components in sepsis [21,22]. We therefore tested whether serum HA might be distinctly regulated in patients with sepsis as well. In fact, we found significantly elevated HA serum concentrations in septic ($n = 96$, median 344 µg/L, range 0–2641 µg/L) versus non-septic etiology of critical illness ($n = 56$, median 141.5 µg/L, range 0–2838 µg/L) in patients without pre-existing liver cirrhosis ($P = 0.004$, data not shown). When patients were divided according to the absence of SIRS ($n = 20$), presence of SIRS ($n = 33$) or presence of sepsis, severe sepsis or septic shock ($n = 97$), patients with septic conditions had highest HA serum values, while the difference between non-SIRS (median 115.5 µg/L, range 10–2457) and SIRS patients (median 168 µg/L, range 0–2117) did not reach statistical

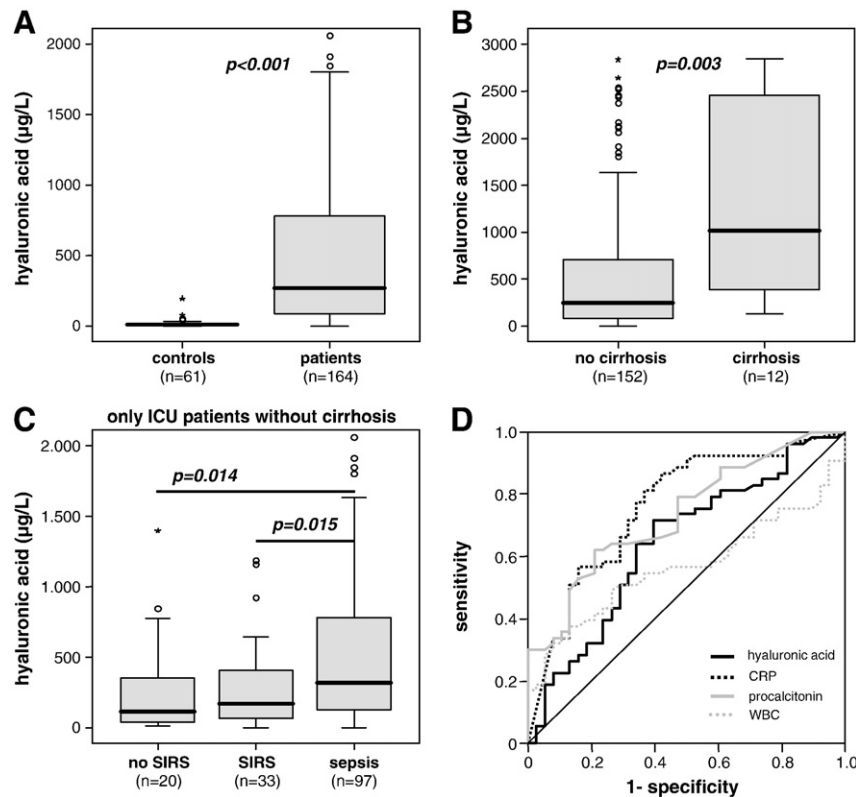


Fig. 1. Serum hyaluronan concentrations in critically ill patients at ICU admission. (A) Serum hyaluronan concentrations at admission to the medical ICU were significantly ($P < 0.001$, U-test) elevated in critically ill patients ($n = 164$) as compared with healthy controls ($n = 61$). (B) In patients with liver cirrhosis ($n = 12$) HA serum concentration was significantly ($P = 0.003$) higher as compared with patients without pre-existing liver cirrhosis ($n = 152$). (C) In ICU patients without liver cirrhosis, septic patients had higher HA serum concentrations compared to non-septic patients with ($P = 0.015$) or without systemic inflammatory response syndrome (SIRS, $P = 0.014$). Box plots are displayed, where the bold line indicates the median per group, the box represents 50% of the values, and horizontal lines show minimum and maximum values of the calculated non-outlier values; asterisks and open circles indicate outlier values. (D) Receiver operating characteristic (ROC) curve analyses comparing diagnostic power in predicting sepsis of HA in critically ill patients (black line, area under the curve (AUC) 0.644) with classical markers of inflammation and bacterial inflammation: C-reactive protein (CRP; black dotted line, AUC = 0.762), procalcitonin (PCT; gray line, AUC = 0.735), and white blood cell count (leukocytes; gray dotted line, AUC = 0.567).

significance (Fig. 1C). However, serum HA had inferior diagnostic value to predict the presence of sepsis (AUC 0.644, 95%-CI 0.527–0.760) as compared with routinely used clinical parameters, such as C-reactive protein (AUC 0.762, 95%-CI 0.660–0.863), procalcitonin (0.735, 95%-CI 0.634–0.836) or white blood cell count (0.567, 95%-CI 0.449–0.685, Fig. 1D).

Hyaluronan serum levels correlate with biomarkers of organ dysfunction and inflammation

To determine the factors possibly promoting elevated serum HA levels in critically ill patients, correlation analyses with extensive sets of laboratory parameters were performed. Serum HA concentrations were correlated to biomarkers reflecting (i) hepatic biosynthetic capacity, namely inversely to albumin (Fig. 2A), inversely to pseudo-cholinesterase activity (Fig. 2B) or positively with international normalized ratio (INR), (ii) cholestasis such as positive correlations to bilirubin, gamma-glutamyltranspeptidase (GGT) or alkaline phosphatase activities, and (iii) hepatic inflammation as expressed by positive associations with alanine and aspartate aminotransferase activities (ALT/AST) (Table 3).

Furthermore, with regard to organ function we could also show an association with renal function as displayed by a significant inverse correlation with the glomerular filtration rate of cystatin C (Fig. 2C). Markers of inflammation and bacterial infection, such as procalcitonin (Fig. 2D), C-reactive protein and interleukin-6 were also correlated to HA (Table 3). These findings suggest that elevation of HA serum concentrations is linked to both septic-inflammatory conditions and organ dysfunction in critical illness, which are considered major determinants of clinical outcome in intensive care medicine [23].

Association of HA with clinical scores, ICU treatment measures and mortality

Based on the observed association between serum HA, inflammation and organ dysfunction, we hypothesized that HA could be useful in clinical practice to predict the prognosis of ICU patients. Indeed, we found a significant correlation between HA serum concentrations and the Sequential Organ Failure Assessment (SOFA) score ($r=0.278$, $P=0.001$) as an established clinical score for multi-organ failure at the ICU, suggesting that HA levels are closely linked to disease severity in critical illness. This result was corroborated by correlations between HA and therapeutically required ICU treatment measures such as fluid administration ($r=0.230$, $P=0.003$), total net volume demand during the first 24 h ($r=0.299$, $P=0.008$) and vasopressor dosage ($r=0.330$, $P=0.013$). Additionally, HA showed a strong correlation to soluble urokinase plasminogen activator receptor (suPAR) ($r=0.585$, $P\leq 0.001$), which we had recently identified as a stable and robust predictive marker in critically ill patients to assess mortality risk [17].

Although these data revealed a close association of HA levels with disease severity and extent of required therapeutic interventions, HA concentrations at ICU admission did not differ between patients that subsequently survived critical illness or that died during the course of ICU treatment (Fig. 3A). Hyaluronan measurements were also not associated with survival upon Cox regression analysis (data not shown). Furthermore, HA levels at ICU admission from either the highest quartile (HA > 779 $\mu\text{g/L}$) or the lowest quartile (HA < 87.5 $\mu\text{g/L}$) did not predict ICU mortality of critically ill patients, as depicted by Kaplan–Meier curves (Fig. 3B). This suggests that severe inflammatory and metabolic disturbances at ICU admission as reflected by elevated HA levels in critically ill patients do not necessarily translate

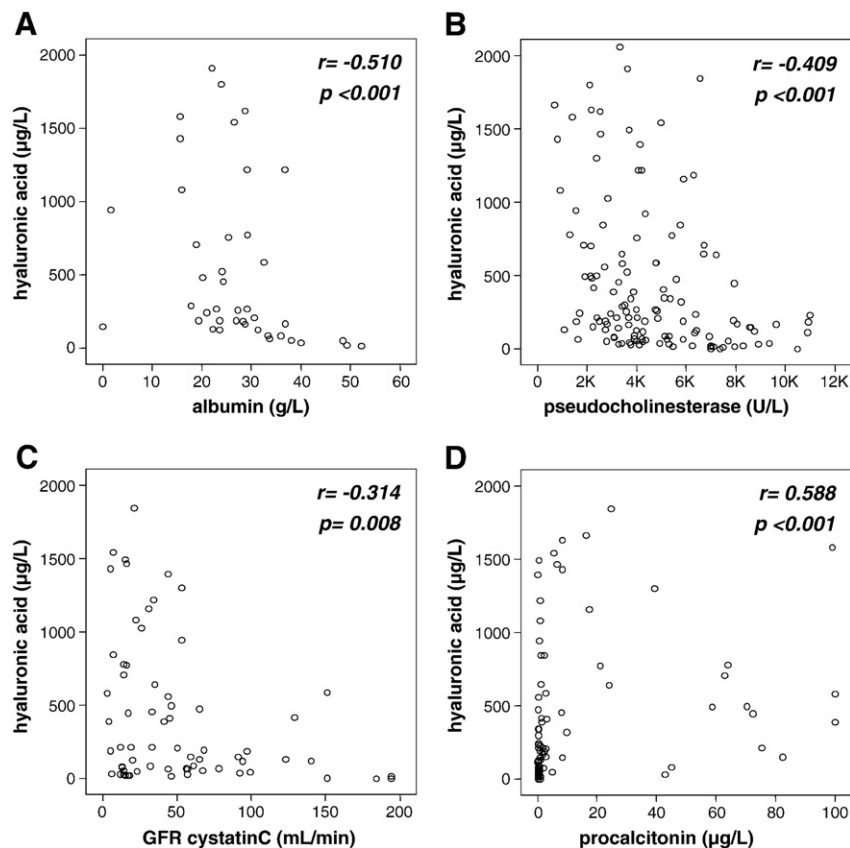


Fig. 2. Association of hyaluronan with organ dysfunction and inflammation in critically ill patients. Hyaluronan serum concentrations correlate inversely with liver synthesis function as displayed by serum albumin (A) and pseudo-cholinesterase activity (B), inversely with renal function ((C), glomerular filtration rate [GFR] for cystatin C) and positively with procalcitonin (D). Correlation coefficient and *P*-values are given in the figure.

Table 3

Correlations between hyaluronan serum concentrations and laboratory/clinical parameters at admission day.

Parameters	ICU patients	
	r	P
Markers of liver function		
PCHE	−0.409	<0.001
Protein	−0.364	<0.001
Albumin	−0.510	<0.001
INR	0.534	<0.001
AST	0.367	<0.001
ALT	0.211	0.007
Bilirubin	0.401	<0.001
Bilirubin conjugated	0.606	<0.001
yGT	0.311	<0.001
AP	0.215	0.010
Markers of inflammation		
CRP	0.383	<0.001
Procalcitonin	0.588	<0.001
IL-6	0.344	0.004
IL-10	0.383	0.001
Markers of renal function		
Cystatin C	0.325	0.006
Cystatin C GFR	−0.314	0.008
Others variables		
Glucose	−0.283	<0.001
Lactate	0.215	0.006
Calcium	−0.311	<0.001
Cholesterol	−0.347	<0.001
Platelets	−0.424	<0.001
suPAR	0.585	<0.001
NTproBNP	0.251	0.002
NTproCNP	0.314	0.004
Clinical scoring and ICU treatment measures		
SOFA score	0.278	0.001
Fluid administration	0.230	0.003
Total volume demand (initial 24 h)	0.299	0.008
Vasopressor dosage	0.330	0.013

r, correlation coefficient; P, P-value; r and P-values by Spearman rank correlation; ALT/AST, alanine/aspartate aminotransferase; AP, alkaline phosphatase; CRP, C-reactive protein; GFR, glomerular filtration rate; yGT, gamma-glutamyl-transferase; IL, interleukin; INR, international normalized ratio; NTproBNP/CNP, N-terminal pro-brain / pro-C-type natriuretic peptide; PCHE, pseudocholinesterase; suPAR, soluble urokinase plasminogen activator receptor; and SOFA, sequential organ failure assessment.

into adverse clinical outcomes, likely due to initiated intensive treatment measures, including anti-infective therapy, fluid challenge and hemodynamic support.

Discussion

Hyaluronic acid (HA) has long been investigated as a potentially central molecule in critical care medicine, due to its association with

liver diseases [8] and sepsis [11,12]. More recently, direct immunological functions of HA by regulating inflammatory cell recruitment, release of inflammatory cytokines, and cell migration have been proposed [3]. This prompted us to revisit the role of HA in a large, well characterized cohort of critically ill patients at a medical ICU in a prospective manner. In this study, we show that HA serum concentrations are significantly elevated in critically ill patients compared to healthy controls, with highest levels in pre-existing liver cirrhosis and also in sepsis. The close association between liver dysfunction and serum HA was anticipated, confirming previously reported mechanisms of HA turnover and catabolism in blood circulation [1]. Circulating HA is believed to be primarily taken up by the liver and degraded after endocytosis by sinusoidal endothelial cells [7,24]. As such, HA binds to HARE (hyaluronan receptor for endocytosis) or LYVE1 (lymphatic vessel endothelial hyaluronan receptor 1) on hepatic endothelium [25]. In case of liver dysfunction, circulating HA levels are increased by enhanced production by activated hepatic stellate cells (the major collagen-producing cells in hepatic fibrosis) and by decline of hepatic elimination by the liver endothelial cells [10].

Our study highlighted that, besides liver dysfunction, other factors contribute to elevated HA levels in critically ill patients. We observed an inverse relationship between serum HA and the glomerular filtration rate. Similarly, increased HA levels have also been found in patients with chronic renal failure [26], indicating that HA might be also partially cleared by the kidney [1,27] or that this could be an epiphenomenon due to impaired renal elimination of proinflammatory cytokines, increased synthesis of cytokines in uremia, or an adverse effect of inflammation on renal function by itself [26]. The distinct elevation of HA in sepsis is likely due to impaired hepatic or renal clearance as typical features of severe systemic inflammation, but could also be propagated by sepsis-specific mechanisms such as release from bacterial wall components [21,22]. This assumption might be supported by the close correlation between HA and procalcitonin, an established biomarker for bacterial infections [28].

Interestingly, recent data indicate that HA is involved in regulating inflammatory processes [3]. For instance, HA binds to hyaluronan specific binding protein e.g. CD44, a cell-surface transmembrane glycoprotein. On the one hand, HA–CD44 interactions play an important role in T cell recruitment and activation [29]. On the other hand, ligation of endothelial CD44 with HA mediates neutrophil migration [5,30], and neutrophil CD44–HA interaction can induce elimination of neutrophils from sites of inflammation, including inflammatory kidney or lung diseases [13,31,32]. Overall, many of the HA–CD44 interactions appear to be rather anti-inflammatory [6,13], raising the possibility that the observed elevation of serum HA in our septic patients reflects endogenous counter-inflammatory cascades. Consequently, high-molecular weight

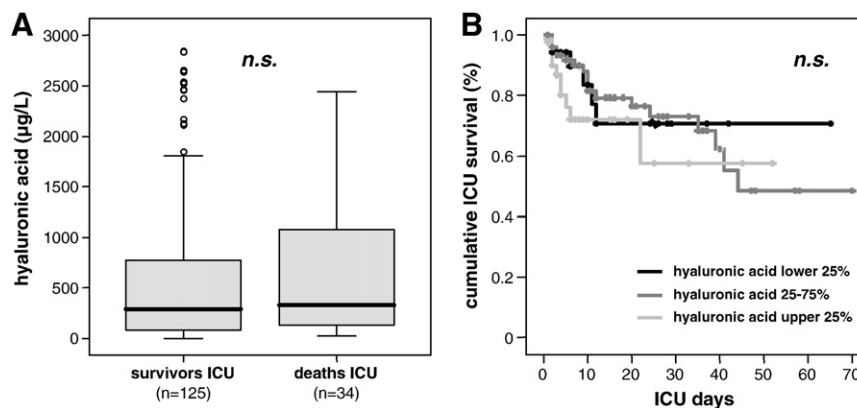


Fig. 3. Association of hyaluronan concentrations at ICU admission with mortality. (A) Serum hyaluronan concentrations at admission to the medical ICU do not differ significantly between patients who survived critical illness (n = 125) and patients who died during the course of ICU treatment (n = 34). (B) Kaplan–Meier survival curves of ICU patients are displayed. HA levels are not associated with ICU mortality in critically ill patients (lowest 25% HA <87.5 µg/L, highest 25% HA > 779 µg/L).

hyaluronan has been suggested as a possible new treatment option for sepsis-induced lung injury and improved outcome in experimental animal models [14,33,34].

From a clinical perspective, serum HA measurements apparently provide information on pre-existing liver fibrosis/cirrhosis, but in patients without underlying liver diseases it rather reflects severity of critical illness. Interestingly, we detected an association between HA and ICU treatment measures such as fluid administration, volume substitution and vasopressor demand, which are all indicators for high therapeutic demand and expectably unfavorable clinical outcome. However, serum HA levels did not indicate mortality of ICU patients. This could fit to the proposed beneficial functions of HA in inflammatory diseases, which had been suggested from animal models, because despite a close association with disease severity, patients with relatively high HA levels did not display an adverse outcome. This overt discrepancy between HA's association with morbidity, but not mortality in critical illness warrants further investigation. Potentially, HA could be involved in the pathogenesis of non-cirrhotic critical diseases and sepsis by exerting regulative functions in tissue injury and repair processes. The possible diagnostic and therapeutic implications of elevated HA in medical ICU patients demand further studies.

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