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Plasma Hyaluronan Decreases During ICU Stay in COVID-19 Survivors but Not in Non-Survivor: A Retrospective Cohort Study

Jaap Van Der Heijden[1*], Constantinos Kolliopoulos[2], Karl Stattin[1], Miklos Lipcsey[1], Robert Frithiof[1], Masood Kamali-Moghaddam[3], Anders Larsson[4], Chun-Yu Lin[2,5], Jyrki Tenhunen[1], Michael Hultström[1,6] and Paraskevi Heldin[2]

[1]Department of Surgical Sciences, Anesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden

[2]Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden

[3]Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Uppsala, Sweden

[4]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden

[5]Department of Internal Medicine, Infection Control Center, Kaohsiung Medical University, Kaohsiung, Taiwan

[6]Department of Medical Cell Biology, Integrative Physiology, Uppsala University, Uppsala, Sweden

[*]**Corresponding author:** Jaap Van Der Heijden, Department of Surgical Sciences, Anesthesiology and Intensive Care, Uppsala University, Uppsala, Sweden, E-mail: jaap.vanderheijden@surgsci.uu.se

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Abstract

Background: Plasma hyaluronan concentration is associated with disease severity in COVID-19 patients. Hyaluronan is found in secretions and alveolar exudate in COVID-19 patients, and increased perialveolar interstitial hyaluronan has been found in the lungs of COVID-19 patients. This may obstruct alveoli and impair gas exchange and thereby contribute to hypoxemia and respiratory failure. The aim of this study was to describe the dynamics of plasma hyaluronan concentrations and to compare hyaluronan concentrations between non-survivors and survivors in critically ill COVID-19 patients.

Methods: An Enzyme Linked Immunosorbent Assay (ELISA)-like assay was used to measure plasma hyaluronan in patients with severe COVID-19 treated in the Intensive Care Unit (ICU) at a tertiary hospital in Sweden (n=19). Measurements were taken early (0-2 days after ICU admission) and late (11-16 days after ICU admission). Plasma hyaluronan levels were compared in patients over time and between 30-day survivors and non-survivors. Plasma of healthy blood donors (n=3) were included for reference.

Results: 30-day mortality was 21% (4/19 patients). Plasma hyaluronan concentrations were higher early during ICU stay (108 ng/ml (IQR 40-321) compared with those at the later stay (22 ng/ml (IQR 2-66), p=.001). Late samples showed higher hyaluronan concentrations in non-survivors compared with that for survivors (91 ng/ml (65-131) vs. 17 ng/ml (0-32), p=.009). Plasma hyaluronan concentrations were similar for patients that acquired a secondary infection compared with those who did not (p=.651).

Conclusion: Plasma hyaluronan levels among COVID-19 patients were higher early after admission to the ICU compared with later during the ICU stay. The plasma hyaluronan concentrations remained higher in non-survivors compared with survivors, indicating that hyaluronan may play a role in both the pathophysiology and severity of COVID-19 infection.

Keywords: Coronavirus; SARS-CoV-2; Hyaluronan; Intensive care

Abbreviations

ALT: Alanine Transaminase; AST: Aspartate Transaminase; b-HABP: Biotinylated Hyaluronan Binding Protein; BMI: Body Mass Index; BSL2: Biosafety Level; CBC: Complete Blood Count; COVID-19: Coronavirus Disease 2019; CRP: C-Reactive Protein; CT: Computerized Tomography; ELISA: Enzyme Linked Immunosorbent Assay; HABP: Hyaluronan Binding Protein; HRP: Horseradish Peroxidase; ICU: Intensive Care Unit; IQR: Interquartile Range; LD: Lactate Dehydrogenase; PaO_2/FiO_2: Arterial Partial Pressure of Oxygen/Fractional Inspired Oxygen; PBS: Phosphate-Buffered Saline; ROS: Reactive Oxygen Species; RT-PCR: Reverse-Transcription Polymerase Chain Reaction; SAPS3: Simplified Acute Physiology Score 3; SOFA: Sequential Organ Failure Assessment; TE: Thromboembolism

Introduction

Coronavirus disease 2019 (COVID-19) has become a worldwide pandemic and a challenge for clinicians and researchers alike. Improvements in both treatment and knowledge of the pathophysiology has been made but much is still unknown. COVID-19 is characterized by inflammation of the lungs causing hypoxemia and respiratory failure. Autopsy studies have found increased lung weight and lungs filled with clear

liquid jelly with the histologic appearance of hyaline membranes [1-5]. Hyaluronan has been found in exudate, plugs and the perialveolar interstitium of the lungs, thereby obstructing alveoli and impairing gas exchange [6]. Respiratory secretions of intubated patients with COVID-19 have a 20-folds higher low-molecular hyaluronan content compared to that in samples from healthy controls [7]. A meta-analysis of RNA sequencing data of pulmonary cells obtained from bronchoalveolar lavage showed that genes encoding enzymes involved in hyaluronan metabolism are upregulated [8]. This growing evidence indicates a new pathogenic mechanism, where hyaluronan may contribute to hypoxemia and respiratory failure in COVID-19 [1,9]. Recently, it was demonstrated that high levels of circulating hyaluronan are correlated with disease severity of patients with COVID-19 [10]. However, the dynamics of plasma hyaluronan concentration throughout disease has not been studied, and no study has compared plasma hyaluronan levels between non-survivors and survivors. The aim of this study was to describe changes in plasma hyaluronan concentration in COVID-19 patients early after Intensive Care Unit (ICU) admission and later during ICU stay, and to compare hyaluronan concentrations between 30-day non-survivors and survivors.

Materials and Methods

Participants and data collection

We included COVID-19 patients who were treated in ICU at Uppsala University Hospital, Sweden, for at least 10 days between March 13th and April 16th 2020. Positive Reverse-Transcription Polymerase Chain Reaction (RT-PCR) was used to confirm COVID-19. Simplified Acute Physiology Score 3 (SAPS3) [11] was calculated on admission followed by daily recording of the Sequential Organ Failure Assessment (SOFA) score [12], respiratory (including PaO_2/FiO_2) and circulatory data. At discharge, vital status and time on invasive ventilation, vasopressor support and renal replacement therapy were noted. Information on secondary infections were also collected. STROBE guidelines were followed for reporting.

Laboratory analysis

Complete Blood Count (CBC), kidney function, liver function, highly sensitive C-Reactive Protein (CRP) and ferritin were recorded on a daily basis as part of routine testing. CBC was analyzed on Sysmex XNTM (Sysmex, Kobe, Japan), while CRP, ferritin, kidney and liver markers were analyzed on Architect ci16200 (Abbott Laboratories, Abbott Park, IL, US). Sodium citrate tubes were collected early, within 2 days after ICU admission and at day 11-16 of ICU stay.

The ELISA-like assay for hyaluronan quantification is based on the specific and irreversible binding of hyaluronan in the samples to immobilized link domain of aggrecan (also termed Hyaluronan Binding Protein, HABP) [13]. In short, COVID-19 patient´s blood samples after transportation to BSL2 laboratory were centrifuged at 3000 rpm for 10 min, at room temperature, and stored at -80°C. On the day of the assay proceeding, the samples were thawed out gradually on ice, and the virus infectivity was inactivated by heating to 56°C for 1 h. Hyaluronan standards (0 ng/ml-50 ng/ml) and patient samples, at appropriate dilutions in PBS containing 1% bovine serum albumin, were added on Maxisorb 96-well Nunc-Immuno plates precoated with 1 µg/ml HABP in 50 mM carbonate buffer, pH 9.5. After an incubation of 1 h, at 37°C, to allow the formation of HABP-hyaluronan complexes, followed by washing, biotinylated HABP (b-HABP) was added, and samples were incubated an additional 1 h. After washing away excess of b-HABP, the b-HABP bound to the hyaluronan trapped by the HABP-coated plates was detected with streptavidin-biotinylated HRP, followed by the substrate solution (3,3',5,5'-Tetramethylbenzidine). The color development in the wells was terminated with 2 M H2SO4, and the absorbance at 450 nm was determined (Enspire Multimode Plate Reader, PerkinElmer).

Statistical analysis

All statistical analyses were performed using IBM® SPSS® statistics version 23 (SPSS, Inc., Chicago, IL, USA). Numerical variables were reported as median (Interquartile Range (IQR) or range) and categorical variables as number of observations (percent of total number of observations). The normality of distribution of continuous variables was tested by Kolmogorov-Smirnov test and visually assessed using histograms. Repeated measurements were compared using Wilcoxon signed-rank test. Kruskal-Wallis test was used when 3 groups were compared. Correlations and independent group analyses were carried out using Spearman Rank and Mann-Whitney U test, respectively. A p-value $p<.05$ was considered statistically significant.

Results

Nineteen patients with COVID-19 admitted to the ICU were included in this study. Median body mass index (BMI) was 30.8 (IQR 27.7-34.3), and all but one patient were men. Twelve patients (63%) had at least one comorbidity, with hypertension or diabetes being the most common. Patients were admitted to the ICU after a median of 9 days (IQR 7-11) of COVID-19 symptoms. SOFA scores were similar early and late during ICU stay (7 (IQR 5-7) vs. 7 (IQR 5-9)). Median length of ICU stay was 18 days (IQR 15-22), and the 30-day mortality after ICU admission was 21% (non-survivors n=4). Characteristics including comorbidities of non-survivors and survivors are presented in **Table 1**. Non-survivors and survivors had similar age and SAPS3 scores on admission. All patients at some point received invasive ventilation and vasopressor support (all were treated with noradrenalin), whereas 4 patients received renal replacement therapy (21%). Early blood samples were taken on average 1 day after ICU admission (range 0-2 days) and late samples were taken on average on day 12 in the ICU (range 11-16).

	All	Non-survivors	Survivors
	n=19	n=4	n=15
Male, n (%)	18 (95)	4 (100)	14 (93)
Age	59 (40-73)	74 (73-76)	55 (39-69)
Body weight, kg	90 (80-107)	96 (80-112)	90 (80-107)
Height, cm	175 (167-178)	174 (165-178)	174 (165-176)
BMI, kg/m^2	31 (28-34)	29 (24-33)	31 (28-35)
SAPS3	50 (45-58)	55 (48-63)	50 (42-55)
COVID-19 day ICU arrival	9 (8-11)	9 (9-12)	9 (8-11)
Comorbidities, n (%)			
Hypertension	8 (42)	3 (75)	5 (33)
Diabetes mellitus	6 (32)	2 (50)	4 (27)
Pulmonary disease	4 (21)	1 (25)	3 (20)
Peripheral vessel disease	3 (16)	2 (50)	1 (7)
Ongoing steroid treatment	3 (16)	0 (0)	3 (20)
Malignancy	0		
Liver failure	0		
Number of comorbidities, n (%)			
0	7 (37)	2 (50)	5 (33)
1	6 (32)	1 (25)	5 (33)
2	3 (16)	0 (0)	3 (20)
3	3 (16)	1 (25)	2 (13)
≥ 1	12 (63)	2 (50)	10 (67)

Abbreviations: BMI: Body Mass Index; IQR: Interquartile range; SAPS3: Simplified Acute Physiology Score; TE: Thromboembolism. Median (IQR) or n (%)

Table 1: Patient demographic characteristics and comorbidities, all patients, non-survivors (30 days) and survivors (30 days).

The median plasma hyaluronan concentrations of the healthy blood donors was 51 ng/ml (range 27-92). Plasma hyaluronan concentrations among patients with COVID-19 were higher early after admission compared with later during ICU stay (108 ng/ml (IQR 40-321) vs. 22 ng/ml (IQR 2-66), p=.001 (**Figure 1**).

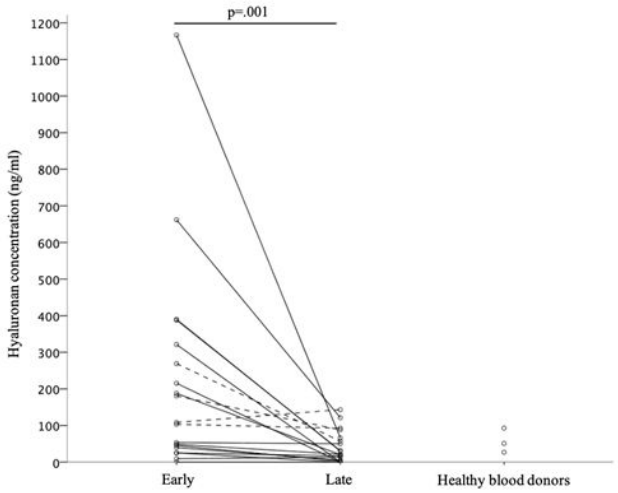

Figure 1: Plasma hyaluronan concentrations (ng/ml) early after admission (n=19), late in the ICU stay (n=19) and healthy blood donors (n=3). Each line represents the dynamics for an individual patient (dashed lines=non-survivors, solid lines=survivors).

There was no difference in plasma hyaluronan concentration between non-survivors and survivors early after admission, but the concentrations remained higher for non-survivors in late samples (**Table 2**).

Plasma hyaluronan concentrations in late samples from patients who acquired a secondary infection (n=15) were similar compared with those who did not. There was no correlation between early plasma hyaluronan concentration and SAPS3 or SOFA score for the corresponding day, whereas late plasma hyaluronan did not significantly correlate with same-day SOFA score in this small sample. There was no difference in either early or late plasma hyaluronan concentration in patients who

	Early		Late			Healthy blood donors		
	Median (IQR)	n	Median (IQR)	n	p-value	Median (IQR)	n	p-value
Hyaluronan (ng/ml)								
All	108 (40-321)	19	22 (2-66)	19	.001*	51 (39-72)	3	.01†
Non-survivor	145 (105-247)	4	91 (65-131)	4	.273*			
Survivor	53 (25-387)	15	17 (0-32)	15	.002*			
p-value	.689§		.009§					

Abbreviations: *Early vs. late, p-value from Wilcoxon signed-rank test; † early vs. late vs. healthy blood donors, p-value from Kruskas-Wallis test; § non-survivor vs. survivor, p-value from Mann-Whitney U test; IQR: Interquartile range

Table 2: Hyaluronan concentration of early vs. late vs. healty blood donors.

received renal replacement therapy compared with those that did not. No correlation was found between either early or late plasma hyaluronan concentration and corresponding liver enzymes, bilirubin and creatinine plasma concentrations (**Table 3**).

	Hyaluronan early		Hyaluronan late	
	Rs	**p-value**	**Rs**	**p-value**
ALT (µkat/L)	-.291	.226	-.122	.620
AST (µkat/L)	.222	.361	-.041	.866
LD (µkat/L)	-.095	.699	.195	.439
Bilirubin (µmol/L)	.370	.119	.191	.434
Creatinine (µmol/L)	.063	.798	.158	.518

Abbreviations: Correlation coefficient (Rs) and P-value from Spearman's Rank Order correlation; ALT: alanine transaminase, AST: aspartate transaminase, LD: Lactate Dehydrogenase

Table 3: Correlation between hyaluronan (early/late) and clinical biochemistry.

The PaO_2/FiO_2 ratio increased over time from early after ICU admission to later during ICU stay (21 (IQR 16-24) vs. 23 (IQR 21-33), p=.034). There was no difference in PaO_2/FiO_2 ratio at admission between non-survivors and survivors, but later during ICU stay the PaO_2/FiO_2 ratio remained low for non-survivors compared with survivors (p=.001). No correlation was found between early and late plasma hyaluronan concentration and corresponding PaO_2/FiO_2 ratio. Furthermore, no difference was found between non-survivors and survivors during late ICU stay for liver enzymes, bilirubin and creatinine plasma concentrations (**Table S1**).

Discussion

In this study of 19 critically ill COVID-19 patients, plasma hyaluronan levels decreased during ICU stay among survivors but remained higher among non-survivors. Plasma hyaluronan concentrations of the healthy blood donors in the present study were similar compared with previous studies [14-16]. In the present study, plasma hyaluronan concentration in COVID-19 patients early after ICU admission was high with a considerable variation. An earlier study that compared mildly, severely and critically ill patients with COVID-19 found an increase in plasma hyaluronan concentration with COVID-19 severity [10]. In that study, all patients in the critical group were admitted to the ICU and expressed the highest plasma hyaluronan concentration. The reported hyaluronan concentrations were higher compared to our results. However, they used another analytical method and had no healthy controls making direct comparison difficult.

Several mechanisms such as changes in production, transport or clearance can alter plasma hyaluronan concentrations. Hyaluronan is synthesized by three Hyaluronan Synthases (HAS 1-3) at the plasma membrane, and exported into the Extracellular Matrix (ECM). Inflammation increases the hyaluronan production leading to increased hyaluronan levels in the ECM [17,18] causing accumulation of hyaluronan in Acute Respiratory Distress Syndrome (ARDS) [19]. COVID-19 patients express high levels of pro inflammatory cytokines in the lungs [20], which might contribute to the high levels of hyaluronan found in autopsy studies [6] and respiratory secretions [7]. Secondary infections were not associated with increased plasma hyaluronan in our data and therefore we do not believe that additional bacterial or fungal infection in non-survivors is driving the difference.

Hyaluronan is degraded by Reactive Oxygen Species (ROS) and specific hyaluronidases in tissues and lymphatic pathways [21]. Normal lymphatic function is necessary to maintain a balance between production and clearance of hyaluronan. A substantial amount of hyaluronan is turned over in the lymphatic system itself, while the remaining hyaluronan is transported into the circulation [22]. Mediastinal lymph node enlargement is not considered a typical CT finding in COVID-19 patients, but lymphadenopathy may be underreported in radiological studies [23]. Autopsy reports of COVID-19 patients have shown pathological changes in hilar lymph nodes including congestion, which may be consistent with high hyaluronan concentrations. Changes in the lymphatic system may thus occur in COVID-19 and might contribute to stagnation of hyaluronan in the lungs [5,24]. The removal of hyaluronan from the circulation is very efficient and primarily takes place in the liver by sinusoidal endothelial cells. Plasma hyaluronan concentration is elevated in liver failure, and is a good marker for disease severity [25]. COVID-19 is associated with elevated liver enzymes and liver dysfunction, particularly in critically ill patients [26]. This study found no correlation between plasma hyaluronan concentration and liver enzymes, neither early after admission at the ICU nor at later stay, making it unlikely that liver dysfunction was affecting plasma hyaluronan concentration in this cohort. In addition, some hyaluronan is cleared in the kidneys but since no association was found with this probably is not an important factor in the present study.

The plasma hyaluronan concentrations reported are relatively low compared to other infectious such as influenza A, sepsis and dengue fever [14,27,28]. However, plasma concentration might not accurately reflect interstitial levels of hyaluronan. Accumulation of hyaluronan in tissues with limited lymph drainage, such as the alveolar space or changes in lymphatic flow, may result in stagnation of hyaluronan and diminished transport of hyaluronan into the circulation.

Our study had several limitations. The number of patients in this study is limited and this may increase the risk of type II error. Yet given the pilot nature of this study many of these findings are important to report. This study included patients that had been treated at the ICU for at least 13 days, thus excluding patients discharged from the ICU before day 13 and patients that died before day 13. Measuring plasma hyaluronan levels in these patients may yield additional insights.

Conclusion

This is the first study describing dynamics of plasma hyaluronan concentration in critically ill COVID-19 patients. The findings showing high plasma hyaluronan at ICU admission that do not decrease in patients who die, but normalize in survivors. Neither secondary infection, liver-nor renal failure were associated with differences in late plasma hyaluronan concentrations. Our finding strengthens the growing evidence that hyaluronan may play a role in the pathogenesis and severity of disease of respiratory failure in COVID-19. Further studies are warranted to confirm these findings and to determine which mechanisms contribute to the increased hyaluronan concentrations in plasma and the lungs, and determine if these may be amenable to pharmacological treatment.

Ethics Approval and Consent to Participate

The present study is a sub study of a prospective observational cohort study approved by the National Ethical Review Agency (COVID-19 patient samples; EPM; no. 2020-01623) and by the Regional Ethics Committee at Uppsala University (healthy blood donor samples; Ups-01-367). Informed consent was obtained from the patient or next of kin if the patient was unable to give consent. The declaration of Helsinki and its subsequent revisions were followed.

Consent for Publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author, JvdH. The data are not publicly available due to containing information that could compromise the privacy of research participants.

Competing interests

The authors declare that they have no competing interests

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Authorship contributions

All authors participated in conception and design of the study. CK performed biochemical analyses. All authors had access to the data and participated in data collection and interpretation. JvdH drafted the manuscript, and all authors contributed to manuscript revision. All authors read and approved the final manuscript.

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References

1. Mong MA, Awkal JA, Marik PE (2020) Accelerated hyaluronan concentration as the primary driver of morbidity and mortality in high-risk COVID-19 patients: With therapeutic introduction of an oral hyaluronan inhibitor in the prevention of “Induced Hyaluronan Storm” Syndrome. MedRxiv.
2. Xu Z, Shi L, Wang Y, Zhang J, Huang L, et al. (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 8: 420–2.
3. Tian S, Xiong Y, Liu H, Niu L, Guo J, et al. (2020) Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol 33: 1007-1014.
4. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S (2020) COVID-19 Autopsies, Oklahoma, USA. Am J Clin Pathol 153: 725–33.
5. Liu Q, Shi Y, Cai J, Duan Y, Wang R, et al. (2020) Pathological changes in the lungs and lymphatic organs of twelve COVID-19 autopsy cases. Natl Sci Rev 7: 1868-1878.
6. Hellman U, Karlsson MG, Engström-Laurent A, Cajander S, Dorofte L, et al. (2020)Presence of hyaluronan in lung alveoli in severe Covid-19- an opening for new treatment options? J Biol Chem 295: 15418-15422.
7. Kaber G, Kratochvil MJ, Burgener EB, Peltan EL, Barlow G, et al. (2020) Hyaluronan is abundant in COVID-19 respiratory secretions. MedRxiv.
8. Andonegui-Elguera S, Taniguchi-Ponciano K, Gonzalez-Bonilla CR, Torres J, Mayani H, et al. (2020) Molecular alterations prompted by sars-cov-2 infection: induction of hyaluronan, glycosaminoglycan and mucopolysaccharide metabolism. Arch Med Res 51: 645–53.
9. Shi Y, Wang Y, Shao C, Huang J, Gan J, et al. (2020)COVID-19 infection: The perspectives on immune responses. Cell Death Differ 27: 1451–4.
10. Ding M, Zhang Q, Li Q, Wu T, Huang Y (2020) Correlation analysis of the severity and clinical prognosis of 32 cases of patients with COVID-19. Respir Med 167: 105981.
11. Moreno RP, Metnitz PGH, Almeida E, Jordan B, Bauer P, et al. (2005) SAPS 3--From evaluation of the patient to evaluation of the intensive care unit. Part 2: Development of a prognostic model for hospital mortality at ICU admission. Intensive Care Med 31: 1345–55.
12. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, et al. (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22: 707–10.
13. Li L, Asteriou T, Bernert B, Heldin C-H, Heldin P (2007) Growth factor regulation of hyaluronan synthesis and degradation in human dermal fibroblasts: importance of hyaluronan for the mitogenic response of PDGF-BB. Biochem J 404: 327–36.
14. Sallisalmi M, Tenhunen J, Kultti A, Tammi M, Pettilä V (2014) Plasma hyaluronan and hemorheology in patients with septic

shock: A clinical and experimental study. Clin Hemorheol Microcirc 56: 133–44.

15. Anand D, Ray S, Srivastava LM, Bhargava S (2016) Evolution of serum hyaluronan and syndecan levels in prognosis of sepsis patients. Clin Biochem 49: 768–76.
16. Yagmur E, Koch A, Haumann M, Kramann R, Trautwein C (2012) Hyaluronan serum concentrations are elevated in critically ill patients and associated with disease severity. Clin Biochem 45: 82–7.
17. Berg S (1997) Hyaluronan turnover in relation to infection and sepsis. J Intern Med 242: 73–7.
18. Petrey AC, de la Motte CA (2014) Hyaluronan, a crucial regulator of inflammation. Front Immunol 5: 101.
19. Hällgren R, Samuelsson T, Laurent TC, Modig J (1989) Accumulation of hyaluronan (hyaluronic acid) in the lung in adult respiratory distress syndrome. Am Rev Respir Dis 139: 682–7.
20. Pandolfi L, Fossali T, Frangipane V, Bozzini S, Morosini M, et al (2020) Broncho-alveolar inflammation in COVID-19 patients: A correlation with clinical outcome. BMC Pulm Med 20: 301.
21. Bourguignon V, Flamion B (2016) Respective roles of hyaluronidases 1 and 2 in endogenous hyaluronan turnover. FASEB J 30: 2108–14.
22. Fraser JR, Kimpton WG, Laurent TC, Cahill RN, Vakakis N (1988) Uptake and degradation of hyaluronan in lymphatic tissue. Biochem J 256: 153–8.
23. Valette X, du Cheyron D, Goursaud S (2020) Mediastinal lymphadenopathy in patients with severe COVID-19. Lancet Infect Dis 20: 1230.
24. Menter T, Haslbauer JD, Nienhold R, Savic S, Hopfer H, et al. (2020) Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. Histopathology 77: 198–209.
25. Gudowska M, Gruszewska E, Panasiuk A, Cylwik B, Flisiak R, et al. (2016) Hyaluronic acid concentration in liver diseases. Clin Exp Med 16: 523–8.
26. Jothimani D, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M (2020) COVID-19 and the liver. J Hepatol 73: 1231–40.
27. Lin C-Y, Kolliopoulos C, Huang C-H, Tenhunen J, Heldin C-H, et al. (2019) High levels of serum hyaluronan is an early predictor of dengue warning signs and perturbs vascular integrity. EBioMedicine 48: 425–41.
28. Engström-Laurent A, Lööf L, Nyberg A, Schröder T (1985) Increased serum levels of hyaluronate in liver disease. Hepatology 5: 638–42.