Letter to the Editor

SARS-CoV-2/COVID-19

Alpha-1 antitrypsin as a risk marker in SARS-CoV-2 infection

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The SARS-CoV-2 virus has infected millions of people worldwide. Given its unpredictability, much research is being focused on potential indicators of a poor course of the resulting disease, COVID-19. Various serum biomarkers, e.g., total leukocyte and lymphocyte counts, lactate dehydrogenase (LDH), D-dimer, procalcitonin, troponin I and ferritin levels, seem to provide support for decision making on process severity and the need of intensive care unit (ICU) transfer, and even predict mortality [1, 2].

Alpha-1 antitrypsin (AAT) is a water-soluble glycoprotein, mainly synthesised by hepatocytes, and provides the largest part of anti-protease activity to the human body. Being an acute phase reactant, its plasma levels increase in response to inflammatory or infectious stimuli and persist for 7 to 15 days [3]. In addition to its anti-inflammatory activity, AAT has anti-microbial properties, as its carboxy-terminal 20 amino-acid residues can interfere with virus replication and infectivity, e.g., of the human immunodeficiency virus [4]. A similar response could be expected in SARS-CoV2-infected patients, although only a few studies have focused on this aspect so far.

Accordingly, we wanted to explore AAT levels as a potential risk marker for severe SARS-CoV-2 infections with a poor course. To this end, a prospective, observational, descriptive study was performed on patients admitted consecutively to our hospital with SARS-CoV-2 pneumonia. The study was conducted in accordance with the Declaration of Helsinki and approved by the hospital's ethics committee. Diagnosis was established through real-time, reverse polymerase chain reaction (RT-PCR) for SARS-CoV-2 in samples from nasopharyngeal smears, paralleled by lung consolidation on current chest radiography. The criteria inclusion comprised AAT, LDH, ferritin, D-dimer, total lymphocyte count, C-reactive protein and interleukin 6 (IL-6) determination in all patients within 48 h after admission, an RT-PCR confirmed diagnosis and radiological diagnoses pneumonia. Patients in whom some of the established measurement parameters were missing, or performed later than 48 h after admission, as well as patients who did not present radiological infiltrates on admission were discarded. Emerging adult respiratory distress syndrome (ARDS), determined by pulse oximetric saturation/fraction of inspired oxygen ratio (SpO_2/FiO_2) < 300 [5], was considered the reference parameter for a poor disease course.

The study sample consisted of 45 patients; 37.8% were women and 62.2% men. Their median age was 59 ±11.49 years. The mean time from onset of symptom to hospital admission was 5.12 ±3.48 days; 37.8% of

Table I. Blood serum parameters in patients with SARS-CoV-2 pneumonia

Parameter	TOTAL (n = 45)		No ARDS		ARDS		*P*-value
	Mean (95% CI)	Median (Q1–Q3)	Mean (95% CI)	Median (Q1–Q3)	Mean (95% CI)	Median (Q1–Q3)	
AAT [mg/dl]	186.2 (170.2–202.1)	191 (138–228.5)	161.8 (142.9–180.7)	148.5 (131.5–188.5)	226.4 (210.2–242.6)	226 (206–242.5)	< 0.001
LDH [U/l]	310.6 (276.4–344.8)	275 (237.5–395.5)	274.9 (241.5–308.4)	268 (191.3–328)	396.3 (302–436.5)	345 (249.5–435.5)	0.019
Ferritin [ng/ml]	1062.9 (707.8–1418.1)	833 (337.5–1307.5)	1001.3 (453.2–1549.3)	586 (307.8–1215)	1164.5 (818–1510.9)	1090 (691.5–1553.5)	0.049
Lymphocytes [× 10^6/l]	1767.9 (1123.9–2411.9)	1420 (940–1940)	2009.1 (979.8–3038.4)	1455 (907.5–1995)	1370.6 (1016.4–1724.7)	1210 (955–1660)	0.520
D-dimer [ng/ml]	3140.8 (67.2–6214.3)	548 (296–1092.5)	612.4 (393.7–831)	386 (199.5–876.5)	7305.1 (-948.1–15558.3)	1210 (955–1660)	0.012
IL-6 [pg/ml]	98.9 (-9.6–207.5)	14.8 (4.7–50.1)	25.8 (10.6–41)	11.3 (4.8–4.6)	219.4 (-76.7–515.5)	44.5 (4.3–143.3)	0.232

ARDS – adult respiratory distress syndrome, CI – confidence interval, AAT – α1-anti-trypsin, LDH – lactate dehydrogenase, IL-6 – interleukin 6. P-value corresponds to non-parametric Mann-Whitney U-test.

the patients developed ARDS, 11.11% eventually needed transfer to the ICU. The overall mortality was 2.22%. Patients who developed ARDS had significantly higher levels of AAT, LDH, ferritin and D-dimer than the rest (Table I). AAT levels > 200 mg/dl, i.e. above the upper reference level, correlated with emerging ARDS with an odds ratio (OR) of 30.9 (95% confidence interval (95% CI): 3.17–301.55). Applying multivariate analysis, only AAT correlated significantly (in 82.2% of the cases) with ARDS (OR = 1.026, 95% CI: 1.004–1.047).

Only a few studies have assessed AAT in SARS-CoV-2 infection so far. McElvaney *et al.* [6] reported a higher IL-6/AAT ratio in patients who needed ICU transfer than in subjects with a more favourable disease course.

Other authors, such as Wettstein *et al.* [7], have demonstrated *in vitro* that AAT is capable of inhibiting SARS-CoV-2 replication in infected cells. These cells increase serine transmembrane protease 2 (STP2) expression, which in turn has an anti-inflammatory effect that facilitates virus entry into the cells. AAT appears to act by inhibiting STP2, thus hampering viral uptake. Our study indicated that AAT levels > 200 mg/dl constitute an important predictor of ARDS and thus a potential means for patient monitoring.

To date, only a few studies have evaluated AAT as a prognostic marker. Age, comorbidities, lymphopenia, increased inflammatory biomarkers (e.g., C-reactive protein, serum ferritin and erythrocyte sedimentation rate) and elevated aspartate aminotransferase, creatinine and LDH levels have been correlated with ARDS in patients with COVID-19 [8].

In conclusion, the results of our study indicate that AAT may be a reliable marker in predicting the occurrence of ARDS and therefore the disease course in patients affected by SARS-CoV-2, although further studies with a larger sample size are needed to confirm these findings.

Conflict of interest

The authors declare no conflict of interest.

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