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LETTER TO THE EDITOR

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Serum concentrations of Krebs von den Lungen-6 in different COVID-19 phenotypes

Dear Sir,

We thank Nakamura et al[1] for sharing their clinical results on the glycoprotein Krebs von den Lungen-6 (KL-6) in differential phenotyping of COVID-19 patients. It is currently accepted that KL-6, a human mucin protein expressed by type 2 pneumocytes, is a biomarker of several interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis. Our research group recently reported increased serum concentrations of KL-6 in critically ill COVID-19 patients who required mechanical ventilation or intensive care.[2] Nakamura et al[3] measured serum concentrations of KL-6 in two groups of patients with different COVID-19-related acute respiratory distress syndrome phenotypes: type L (spared lung compliance) and type H (low lung compliance). They also recorded serial KL-6 measurements in a type L and a type H patient. The latter showed elevated KL-6 concentrations at admission, in line with our previous data. The former, type L, required extracorporeal membranous oxygenation (ECMO) and serum KL-6 remained in the normal range throughout clinical course (131-363 U/mL).

In line with these results, the Japanese working group *ECMO network for COVID-19* investigated patients with type L COVID-19 treated with ECMO without finding elevated serum concentrations of KL-6, but did not study serial variations in KL-6.[4] However, ECMO works by temporarily drawing blood from the body to allow artificial oxygenation of red blood cells and removal of carbon dioxide. This supporting therapy (that can be implemented by different approaches) could distort serum concentrations of KL-6 because it alters pulmonary circulation: it may, therefore, be incorrect to compare this biomarker in ECMO and non-ECMO patients. Only two articles have addressed this issue of ECMO and KL-6, so there are few results to compare with these findings.[3,4] To help fill this gap, we measured serum concentrations of KL-6 of our COVID-19 patients, divided according to L and H phenotype. Of our 22 COVID-19 patients [median age (IQR) 63 (59-68) years, 16 males] hospitalized at Siena University Hospital, 8 [median age (IQR) 65 (62-68), 6 males] required intensive care and endotracheal intubation. Two (2/8, 25%) were identified as H type and showed median KL-6 concentrations of 888 U/ml (IQR, 776-1000), while six L-type patients (6/8, 75%) showed median KL-6 values of 770 U/mL (IQR, 334-1415).

The severity of the cytokine storm syndrome could affect serum concentrations of KL-6. At admission, serum levels of lactate dehydrogenase (LDH), ferritin and C-reactive protein (CRP) were 371 U/L, 881 ng/mL, and 12.85 mg/dL for H-type patients, whereas L-type patients with had median LDH 314 U/L (IQR, 241-587), ferritin 1567 ng/mL (IQR, 707-1606), and CRP 5.1 mg/dL (IQR, 3.6-30.1).

Our statistical analysis did not demonstrate that KL-6 can discriminate different ventilatory phenotypes on the basis of lung compliance assessment in COVID-19 patients, possibly due to our very limited sample sizes.

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