

RESEARCH LETTER

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# YKL-40 as a new promising prognostic marker of severity in COVID infection

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**Keywords:** COVID-19, SARS-CoV-2, YKL-40, Chitinase 3-like 1, Interstitial lung disease

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for a disease named COVID-19, which may be associated with common symptoms or lead patients to intensive care unit (ICU) or death. The severity of the disease is mainly driven by diffuse interstitial lung diseases (ILD). YKL-40 has a pro-mitogenic action on pulmonary fibroblasts, increases the activity of macrophages and is associated with inflammatory disorders, arteriosclerosis and endothelial dysfunction. In ILD, YKL-40 has been described to be associated with the severity of lung diseases and with the risk of death [1–6]. Yet, in COVID-19 infection, YKL-40 serum levels could therefore be of interest for diagnosis and prognosis since it is at the cross-link between vascular and epithelial lung damage, which are typical characteristics of COVID-19 infection. By closing the gap between those two pathological characteristics, we thought that YKL-40 could be of interest a specific biomarker of severe COVID-19 infection.

We thus retrospectively compared serum levels of YKL-40 in a cohort of 103 patients infected by SARS-CoV-2 hospitalized between March 1 and April 29, 2020, with a group of 58 appariated healthy subjects (HS), 26 patients suffering from chronic obstructive pulmonary disease (COPD) and 53 from non-COVID ILD. Measurement of YKL-40 was taken with the MicroVue™ YKL-40 enzyme immunoassay kit during the 3 first days of admission and

retrospectively analyzed and correlated the results with clinical data [ICU admission, acute renal failure (ARF) or multiple organ failure (MOF)].

Median age of COVID-19 positive patients was 69 yo with a male predominancy (67%). A significant proportion of the cohort ( $n = 103$ ) experienced ICU admission (30%), ARF (32%) and MOF (28%).

COVID-19 patients who were admitted in ICU had statistically higher CRP, creatinine, LDH and YKL-40 ( $p < 0.05$ ) (Table 1). The lymphocyte count was not statistically lower ( $p = 0.059$ ) and D-dimers were not higher ( $p = 0.1297$ ) compared to the other group.

COVID-19 patients exhibited higher serum levels of YKL-40 than HS, COPD and ILD ( $p < 0.0001$  for all groups) (Fig. 1). Median serum level of YKL-40 was 206 ng/ml (95–431) in the COVID-19 group, 46 ng/ml (34–67) in the HS subgroup, whereas they were of 60 ng/ml (41–73) in the COPD and 73 ng/ml (42–91) in the ILD groups, respectively.

Patients suffering from more severe diseases had significantly higher YKL-40 values than those who did not experience ICU admission, MOF or ARF ( $p < 0.05$ ,  $p < 0.05$ ,  $p < 0.001$ , respectively). Patients infected by COVID-19 suffering from prior chronic renal failure and chronic cardiopathy were exhibiting an increased serum level of YKL-40 ( $p < 0.0001$  and  $p < 0.001$ , respectively). Death was not statistically correlated to levels of YKL-40 within the COVID-19 patient group ( $p = 0.12$ ).

The area under the ROC curve (AUC) for the discrimination of patients admitted or not to the ICU in association with the levels of YKL-40, the age and the percentage of lesions visible on the thoracic scanner

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**Table 1 Comparison between COVID-19 patients admitted to intensive care or not**

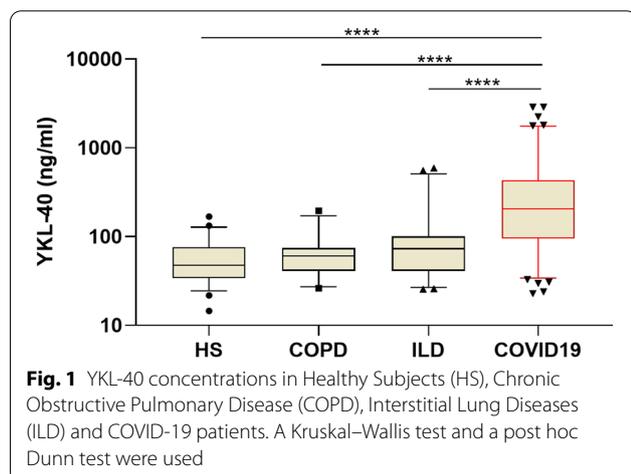
Variables	ICU, No (n = 72)	ICU, Yes (n = 31)	p value
Age (year)	71 (58–82)	65 (59–69)	< 0.05
Gender M/F	44/28	22/9	NS
Height (cm)	169 (162–176)	175 (169–180)	< 0.05
Weight (kg)	71 (63–84)	96 (80–105)	< 0.0001
BMI (kg/m <sup>2</sup> )	25 (22–29)	31 (27–34)	< 0.0001
Abnormal lung lesions (%)	20 (10–35)	40 (30–50)	< 0.001
SpO <sub>2</sub> (%)	93 (89–96)	88 (75–90)	< 0.0001
Death, No/Yes (%)	92.8/7.2	89.3/10.7	NS
Shock or organ failure, No/Yes (%)	91.3/8.7	26.7/73.3	< 0.0001
Cardiopathy, No/Yes (%)	85.5/14.5	75/25	NS
ARF, No/Yes (%)	79.7/20.3	40/60	< 0.001
CRF, No/Yes (%)	85.5/14.5	96.7/3.3	NS
Diabetes, No/Yes (%)	85.5/14.5	62.1/37.9	< 0.05
Red blood cells (× 10 <sup>6</sup> /μl)	4.29 ± 0.79	4.48 ± 0.85	NS
Hematocrit (%)	38 ± 7	39 ± 7	NS
Hemoglobin (g/dl)	13 ± 2	14 ± 2	NS
Globular volume (fl)	89 ± 8	89 ± 7	NS
Reticulocytes (%)	0.97 (0.72–1.15)	1 (0.57–1.04)	NS
Reticulocytes (× 10 <sup>3</sup> /μl)	39 (29–50)	39 (24–51)	NS
Leucocytes (× 10 <sup>3</sup> /μl)	6.15 (4.63–8.03)	7.87 (4.91–13.54)	< 0.05
Blood neutrophils (%)	73 ± 12	78 ± 17	< 0.05
Blood lymphocytes (%)	15 (10–24)	10 (5–20)	< 0.05
Blood monocytes (%)	0.2 (0–0.9)	0 (0–0.1)	< 0.01
Blood eosinophils (%)	7.73 ± 4.36	5.63 ± 3.32	NS
Blood basophils (%)	0.2 (0.2–0.4)	0.2 (0.1–0.3)	NS
Blood neutrophils (10 <sup>3</sup> /μl)	4.54 (3.07–6.4)	6.96 (3.5–11.73)	< 0.05
Blood lymphocytes (10 <sup>3</sup> /μl)	0.96 (0.69–1.27)	0.73 (0.59–1.12)	NS
Blood monocytes (10 <sup>3</sup> /μl)	0.42 (0.25–0.6)	0.37 (0.27–0.6)	NS
Blood eosinophils (10 <sup>3</sup> /μl)	0.01 (0–0.05)	0 (0–0.01)	< 0.05
Blood basophils (10 <sup>3</sup> /μl)	0.01 (0.01–0.02)	0.02 (0.01–0.03)	NS
Platelets (10 <sup>3</sup> /μl)	195 (157–266)	189 (155–252)	NS
Quick time (%)	83 ± 22	83 ± 13	NS
Quick time (s)	13 (12–13)	13 (12–13)	NS
Fibrinogen (g/l)	5.24 ± 1.61	6.06 ± 2.01	NS
D-dimers (μg/L)	876 (517–1787)	1483 (586–2422)	NS
Erythrocytes sedimentation rate (mm/h)	123 (123–123)	48 (48–48)	NS
Iron (μmol/l)	4.27 (2.95–7.36)	4.61 (3.35–7.06)	NS
Ferritin (μg/l)	827 (499–1677)	1861 (889–4117)	< 0.05
Osmolality (mosm/kg)	290 ± 15	286 ± 11	NS
Sodium (mmol/l)	139 ± 5	136 ± 4	< 0.05
Chlorides (mmol/l)	102 ± 6	100 ± 5	NS
Potassium (mmol/L)	4.04 ± 0.44	4.16 ± 0.62	NS
Calcium (mmol/l)	2.23 ± 0.18	2.14 ± 0.21	NS
Phosphates (mg/l)	0.99 ± 0.2	1.15 ± 0.34	NS
Bicarbonates (mmol/l)	24 (21–26)	23 (19–26)	NS
Creatinine (mg/dl)	0.93 (0.8–1.31)	1.25 (0.88–1.6)	0.05
Urea (mg/dL)	41 (31–68)	53 (40–84)	< 0.05
GFR (MDRD) (ml/min/1.73m <sup>2</sup> )	71 ± 33	60 ± 30	NS
Total protein (g/l)	66 ± 8	66 ± 11	NS

**Table 1 (continued)**

Variables	ICU, No (n = 72)	ICU, Yes (n = 31)	p value
Albumin (g/l)	37 ± 5	36 ± 4	NS
Uric acid (mg/dl)	61 ± 25	63 ± 25	NS
CRP (mg/l)	58 (26–144)	166 (105–265)	< 0.0001
Total bilirubin (mg/dl)	0.62 (0.44–0.82)	0.79 (0.53–1.02)	< 0.05
Conjugated bilirubin (mg/dl)	0.25 (0.18–0.34)	0.33 (0.25–0.5)	< 0.05
Alkaline phosphatase (U/l)	75 (59–90)	70 (57–95)	NS
GGT (U/l)	52 (30–111)	64 (29–133)	NS
ASAT (U/L)	35 (24–53)	60 (35–80)	< 0.001
ALAT (U/L)	27 (17–46)	36 (26–56)	< 0.05
LDH (U/l)	310 (244–441)	503 (411–703)	< 0.00001
Lipase (U/l)	32 (19–50)	38 (25–53)	NS
Creatine kinase (U/l)	136 (59–266)	229 (101–426)	0.07
YKL-40 (ng/ml)	186 (84–384)	241 (172–827)	< 0.05

When the data follow a normal distribution, the results are expressed as mean ± standard deviation, and otherwise, they are expressed as the median (IQR)

M, male; F, female; NS, nonsignificant



reached 0.78 ( $p < 0.0001$ ). The positive predictive value was 70%, and the negative predictive value was 83%.

In conclusion, this study showed that firstly the COVID-19 patients had higher levels of YKL-40 compared to a control population (HS, COPD and ILD) and secondly that within the COVID-19 population YKL-40 was an indicator of the seriousness of infection since it is linked to complications such as admission to ICU, ARF or MOF. This marker could also be a predictive marker to anticipate management at the ICU and is useful for the prognosis of the onset of an ILD later. Future studies are also needed to assess the correlation between the levels of YKL-40 and pulmonary sequelae that patients with COVID-19 would develop.

#### Abbreviations

ICU: Intensive care unit; ILD: Interstitial lung diseases; HS: Healthy subjects; COPD: Chronic obstructive pulmonary disease; MOF: Multiple organ failure; AUC: Area under the ROC curve.

#### Acknowledgements

The authors would like to thank the COVID-19 clinical investigators of the CHU de Liège: Ancion, A., Berg, J., Bonhomme, O., Bouquegneau, A., Bovy, C., Bruls, S., Darcis, G., Defraigne, J.O., Ghuysen, A., Gilbert, A., Heinen, V., Lambermont, B., Louis, R., Malaise, O., Martin, M., Misset, B., Moutschen, M., Nguyen Dang, D., Piazza, J., Szecl, D., Szecl, J., Van Cauwenberge, H., Von Frenckell, C., Vroonen, L.

#### Authors' contributions

JG, EC and MH contributed to conceptualization. LS, ANF and MH curated the data. MH contributed to formal analysis. LS and EC contributed to methodology. LS contributed to investigation and writing original draft. EC and JG contributed to supervision, validation, visualization and writing—review and editing. All authors read and approved the final manuscript.

#### Funding

Research grant from Fond Leon Fredericq.

#### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

#### Ethics approval and consent to participate

No specific approval was requested to the ethic committee as a leaflet including the following statement is given to all admitted patients: According to the law of the 19th December 2008, any left-over of biological material collected from patients for their standard medical management and normally destroyed when all diagnostic analyses have been performed, can be used for validation of methods. The law authorizes such use except if the patient expressed an opposition when still alive (presume consent). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. However, for HS, COPD and ILD patients, the protocol was approved by the ethics committee of CHU of Liège, and all subjects gave written consent before their enrollment (Belgian Number: B707201422832; ref: 2014/302).

#### Consent for publication

Not applicable.

### Competing interests

All authors declare to have no specific competing interests for this specific publication.

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Received: 5 November 2020 Accepted: 9 November 2020

Published online: 16 February 2021

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