Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Lipoprotein(a) in COVID-19: Genetics and inflammation collide

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To the Editor,

Accurate prediction of the risk of developing severe illness (i.e., need for mechanical ventilation, intensive care unit admission, up to death) is pivotal in patients with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection, since an appropriate and timely clinical management is highly effective to limit the frequently unfavourable outcome of coronavirus disease 2019 (COVID-19) [1].

Among the various biomarkers that have been proposed so far for predicting the risk of progressing towards severe COVID-19 illness, lipoprotein(a) (Lp(a)) deserves specific focus, due to the potential mechanisms that link its patogeneticity to the course of COVID-19. This life-threatening infectious disease is characterized by a sustained pro-inflammatory state (often referred to as "cytokine storm") [2] and by frequent development of venous and arterial thrombotic episodes [3]. These two events, converging in the co-called process of "thromboinflammation", are also crucial elements in Lp(a) biology, in that this lipoprotein is an acute phase reactant and its concentration is significantly associated with thrombotic risk [4].

Therefore, to summarize the currently available evidence on the possible contribution of Lp(a) to the pathogenesis of COVID-19, we carried out an electronic search in PubMed and Scopus using the keywords "lipoprotein(a)" OR "Lp(a)" AND "COVID-19" OR "SARS-CoV-2" with no language and date limits (i.e., up to February 25, 2022), to identify all clinical studies where Lp(a) concentration was measured in patients with SARS-CoV-2 infection and compared with healthy controls or correlated with the risk of developing COVID-19 related complications. Case reports, reviews or other editorial materials were excluded.

Overall, our search enabled to identify 15 articles, three of which were clinical studies fulfilling our search criteria, as summarized in Table 1.

In an article published in this journal, Nurmohamed et al. measured Lp(a) values in 219 patients hospitalized with COVID-19 [5]. Interestingly, Lp(a) values were found to gradually increase during the first 3 weeks of hospitalization, displaying a substantial correlation with the longitudinal interleukin 6 (IL-6) variation ($r = 0.44$; 95% confidence interval [95%CI], 0.30–0.56; $p < 0.001$). Moreover, COVID-19 patients in the highest tertile of Lp(a) concentration had an over 3-fold higher risk of developing incident venous thromboembolism (VTE) compared to those in the lowest tertile (56.2% *vs.* 18.4%; relative risk [RR], 3.06; 95%CI 1.61–5.81; $p < 0.001$). A trend in predicting major COVID-19 severity (i.e., intensive care unit admission; ICU) was also noted, though such association remained only of borderline statistical significance (RR, 10.90; 95%CI, 0.63–188.04; $p = 0.100$).

In another article, Di Maio et al. conducted a large-scale prospective study including over 500,000 subjects aged between 40 and 69 years recruited up to the year 2010, whose data were compared with those of a second cohort undergoing SARS-CoV-2 testing from March 2020 (55,199 subjects, 13,588 with at least one positive test for SARS-CoV-2) [6]. The incidence of ischemic heart disease in patients with Lp(a) values > 95th percentile (i.e., >220 nm/L) was 489/21755 in the control population and 37/343 in those with SARS-CoV-2 infection, respectively, thus reflecting an over 5-fold enhanced risk in the second cohort (odds ratio [OR], 5.26; 95%CI, 3.70–7.48; $p < 0.001$). Similarly, the incidence of VTE in patients with Lp(a) values > 95th percentile (i.e., >220 nm/L) was 78/21,755 in the control population and 5/360 in those with SARS-CoV-2 infection, respectively, thus reflecting a nearly 4-fold higher risk in the second cohort (OR, 3.91; 95%CI, 1.58–9.73; $p = 0.003$).

In a subsequent study, Lippi et al. measured Lp(a) in 50 patients with COVID-19 and 30 matched sick controls [7]. Interestingly, they first found that serum Lp(a) values in COVID-19 patients at hospital admission did not significantly differ from those of the control sick population (0.1 *vs.* 0.2 g/L; $p = 0.098$), though Lp(a) concentration was found to be a significant predictor of peak disease severity during hospital stay ($r = 0.314$; $p = 0.03$).

Although the limited evidence available so far on the potential impact of Lp(a) on the pathogenesis of COVID-19 does not allow to draw definitive conclusions, some important considerations can be drawn. First, Lp(a) is an acute phase reactant, and its concentration can be consistently boosted during sustained inflammatory states, like that characterizing severe forms of COVID-19 and other acute conditions. This is in keeping with the findings of Nurmohamed et al. [6], who reported a gradual increase of this lipoprotein during hospital stay, directly correlated with IL-6 variations, as well as with those of Lippi et al., who found similar concentrations between patients with COVID-19 and other severely acute diseased states [7]. Then, in all three

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Table 1
Summary of clinical studies which explored the potential impact of lipoprotein(a) in the pathogenesis of COVID-19.

Authors	Study population	Conclusions
Nurmohamed et al., 2022 [5]	219 patients hospitalized with COVID-19	Lp(a) variation significant correlated with concomitant changes of interleukin 6 COVID-19 patients in the highest tertile of Lp(a) concentration had an over 3-fold risk of incident venous thromboembolism compared to those in the lowest tertile
Di Maio et al., 2022 [6]	428,453 control subjects recruited up to 2010 and 55,199 subjects undergoing SARS-CoV-2 testing after March 2020 (13,588 with at least one positive test)	In subjects with Lp(a) > 95th percentile the risk of ischemic heart disease was 5.3-fold higher in subjects with SARS-CoV-2 infection compared to those withou In subjects with Lp(a) > 95th percentile the risk of venous thromboembolism was 3.9 higher in subjects with SARS-CoV-2 infection compared to those without
Lippi et al., 2021 [7]	50 patients with COVID-19 and 30 matched sick controls	Serum Lp(a) values predicted incident peak COVID-19 severity

COVID-19, coronavirus disease 2019; Lp(a), lipoprotein(a); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

studies that we could identified based on our digital search, Lp(a) values both at baseline (e.g., presumably genetically determined) or during illness progression (i.e., boosted by COVID-19 related inflammation) were found to have an impact on clinical outcome of SARS-CoV-2 infection. The most important aspect here concerns the interplay of this lipoprotein with the risk of developing both venous and arterial thrombosis, in that a positive association was found in the studies of Nurmohamed et al. [5] and Di Maio et al. [6] (Table 1).

In conclusion, the evidence emerged from our analysis would lead us to conclude that both baseline and serial Lp(a) assessment shall be part of a routine panel of laboratory tests for COVID-19 monitoring, along with other useful parameters [8].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Martina Montagnana, Giuseppe Lippi*
Section of Clinical Biochemistry, University of Verona, Italy

* Corresponding author. Section of Clinical Biochemistry, University Hospital of Verona, Piazzale L.A. Scuro 10, 37134, Verona, Italy.
E-mail address: giuseppe.lippi@univr.it (G. Lippi).