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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Letter to the Editor: Obesity, diabetes, non-alcoholic fatty liver disease and metabolic dysfunction associated fatty liver disease are proinflammatory hypercoagulable states associated with severe disease and thrombosis in Covid-19

Dear Sir,

Obesity [1,2], diabetes [3,4], non-alcoholic fatty liver disease (NAFLD) [5] and metabolic dysfunction associated fatty liver disease (MAFLD) [6,7] are associated with severe Disease in Covid-19. High incidence (25–70%) of deep vein thrombosis (DVT) had been reported in patients with severe COVID-19, particularly among those admitted to the intensive care units [8–10]. Obesity (BMI ≥30), Padua score > 4 and D-dimer >1.0 (μg/ml) were associated with DVT in COVID-19 patients in multivariant analysis [9,10]. It had been suggested that patients with NAFLD were characterized by a hypercoagulable state, with elevated plasma levels of von Willebrand factor, enhanced platelets activation, and increased levels of circulating plasminogen activator inhibitor type 1 (PAI-1) [11]. It may be possible that the hypercoagulable state in NAFLD contributes to the high incidence of thrombosis in COVID-19 subjects. We retrospectively studied the prevalence of NAFLD among our cohort of COVID-19 patients with doppler ultrasound documented deep vein thrombosis (DVT) [9] and compared the D-dimer levels of NAFLD subjects ($n = 75$) with non-NAFLD subjects($n = 125$) from our previous COVID-19 cohort [5]. NAFLD was identified as hepatic steatosis index more than 36 points from records of the patients before and within 12 months of the diagnosis of COVID-19 and/or by abdominal ultrasound examination. NAFLD was present in 76% (16/21) of COVID-19 DVT subjects as compared with 45% prevalence(27/60) in non-DVT subjects, $p = 0.01$ Alternatively, DVT was detected in 37.2% (16/43) and 13.2% (5/38) of NAFLD and non-NAFLD COVID-19 subjects respectively ($p = 0.01$). The mean admission D-dimers levels of the 21 DVT patients was significantly higher than that of non-DVT subjects (5.20 ± 2.79 μg/ml vs 0.80 ± 1.2 μg/ml, $p < 0.001$). Mean admission and peak D-dimer levels were significantly higher in COVID-19 subjects with NAFLD ($n = 75$) as compared with those without NAFLD ($n = 125$), 0.72 ± 1.10 μg/ml vs 0.38 ± 0.46 μg/ml, $p = 0.003$ and 1.81 ± 4.1 mg/ml vs 0.63 ± 0.41 mg/ml, $p = 0.003$ respectively (Table1). The association of NAFLD with admission and peak D-dimer levels remain significant in multivariate analysis, $p = 0.046$ and $p = 0.028$, respectively. BMI, age > 60, other comorbidities were no longer associated with elevated D-dimer levels at admission in multivariate analysis. The liver is a frontline immune organ and increased production of pro-inflammatory cytokines by adipose and Kupffer cells had been reported in NAFLD patients [12]. During the SARS-CoV-2 infection, there may further increased production of IL6, IL8, TNF-α in NAFLD subjects and higher likelihood of activation of the coagulation cascade by pro-inflammatory cytokines and subsequent thrombosis. Histologic analysis of pulmonary vessels in patients with Covid-19 showed widespread thrombosis with microangiopathy [13]. Lax et al. reported hepatic steatosis, involving 50% to 60% of the hepatocytes, in all 12 COVID-19 patients with pulmonary embolism at autopsies [14]. Similarly, pulmonary thrombi and hepatic steatosis were present in 73% and 55% of COVID-19 patients in an Italian post-mortem series [15]. Obesity and diabetes are also risk factors for NAFLD, MAFLD, and thrombosis. It is possible that these diseases are interlinked and the common pathophysiological pathway for predisposing to severe COVID-19 is a proinflammatory hypercoagulable state contributing to thrombosis and disease progression (Table 1).

Ethical approval and Informed consent

This study was conducted according to the 1975 Declaration of Helsinki and approved by the ethics committee of Union Hospital, the Fifth Medical Center of Chinese PLA General Hospital and Fuyang Second People's Hospital. Written informed consent was waived in view of the status of designated centre for new emerging infectious diseases of the three participating hospitals.

Patients and public involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research.

CRediT authorship contribution statement

DJ, EQ, JX and FW treated the patients and collected the epidemiological and clinical data. DJ, YW, MZ and LZ processed statistical data and drafted the manuscript. GC and GL had the idea for and designed the study. GC, FW and GL revised the final manuscript and are responsible for summarizing all the data.

Declaration of competing interest

We declare no competing interests.

Table 1
Association of VTE with elevation of D-dimers and NAFLD in the UH COVID-19 cohort [9].

	VTE ($n = 21$)	Non-VTE ($n = 60$)	*P* values
D-Dimer levels (μg/ml) at admission	5.2 ± 2.79	0.8 ± 1.2	0.001
BMI	24.6 ± 2.65	23.9 ± 1.9	0.27
NAFLD	76% (16/21)	45% (27/60)	0.01

Association of NAFLD with elevation of D-dimers in the FYSPH -PLAGH COVID-19 cohort [5].

	Non-NAFLD (n = 125)	NAFLD (n = 75)	*p* values (multivariate)
D-Dimer(ug/ml) Admission	0.38 ± 0.46	0.72 ± 1.10	0.003 (0.046)
Peak	0.63 ± 0.41	1.81 ± 4.1	0.003 (0.028)

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References

[1] Palaiodimos L, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx. New York Metabolism. 2020;108:154262. https://doi.org/10.1016/j.metabol.2020.154262 Epub 2020/05/19.

[2] Zheng KI, Gao F, Wang X, Sun Q, Pan K, Wang T, et al. Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease. Metabolism. 2020;108:154244. https://doi.org/10.1016/j.metabol.2020.154244.

[3] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. China medical treatment expert group for C. clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2002032 Epub ahead of print.

[4] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020. https://doi.org/10.1016/S2213-2600(20)30079-5 Feb 24. pii:S22132600.

[5] Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: a retrospective study. J Hepatol. 2020 Apr 8;S0168-8278(20):302063. https://doi.org/10.1016/j.jhep.2020.03.044.

[6] Targher G, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, et al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. Gut. 2020 Aug;69(8):1545–7. https://doi.org/10.1136/gutjnl-2020-321611 [Epub 2020 May 15].

[7] Sharma P, Kumar A. Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19. Diabetes Metab Syndr. 2020 Sep-Oct;14(5):825–7. https://doi.org/10.1016/j.dsx.2020.06.013 [Epub 2020 Jun 10].

[8] Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID19 patients JTH; 2020. https://doi.org/10.1111/JTH.14869.

[9] Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421–4.

[10] Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, et al. Deep vein thrombosis in hospitalized patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: prevalence, risk factors, and outcome. Circulation. 2020. https://doi.org/10.1161/CIRCULATIONAHA.120.046702.

[11] Verrijken AFS, Mertens I, Prawitt J, Caron S, Hubens G, Van Marck E, et al. Prothrombotic factors in histologically proven NAFLD and NASH. Hepatology. 2014;59:121–9.

[12] Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120–8. https://doi.org/10.1056/NEJMoa2015432 [Epub 2020 May 21].

[13] Lax S, Skok K, Zechner P, Kessler H, Kaufman F, Koelblinger C, et al. Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. Ann Intern Med. 2020;173(5):350–61. https://doi.org/10.7326/M20-2566.

[14] Falasca L, Nardacci R, Colombo N, Lalle E, Di Caro A, Nicastri E, et al. Post-mortem findings in italian patients with COVID-19 – a descriptive full autopsy study of cases with and without co-morbidities. The Journal of Infectious Diseases. 2020 Sep 11. https://doi.org/10.1093/infdis/jiaa578.

[15] Braunersreuther V, Viviani GL, Mach F, Montecucco F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. World J Gastroenterol. 2012 Feb 28;18(8):727–35.

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