D-dimers at hospital admission for COVID-19 are associated with in hospital mortality independently of venous thromboembolism: Insight from a French multicenter cohort study

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Abstract

Background: Coronavirus disease 2019 (COVID-19) has been associated with coagulation disorders, in particular high levels of D-dimers, and increased frequency of venous thromboembolism (VTE). We explore the association between D-dimers at admission and in-hospital mortality in hospitalized COVID-19 patients with or without symptomatic VTE.

Methods: From February 26 to April 20, 2020, D-dimer level at admission and outcomes of patients hospitalized for COVID-19 in medical wards (in-hospital mortality or VTE) were retrospectively analyzed in a multicenter study in 24 French hospitals.

Results: Among 2878 patients enrolled in the study, 1154 (40.9%) patients had D-dimer measurement at admission. A receiver operating characteristic (ROC) curve analysis identified D-dimer level above 1128 ng/mL as the optimum cutoff value to predict in-hospital mortality (Area Under the Curve of 64.9% (95% CI 0.60–0.69) with a sensitivity of 71.1% (95% CI 0.62–0.78) and a specificity of 55.6% (95% CI 0.52–0.58) that not differ in the subgroup of patients with VTE during hospitalization. Among 609 (52.8%) patients with D-dimers level < 1128 ng/mL at admission, only 35 (5.7%) deaths occurred during hospitalization. After adjustment, in a cox proportional hazard and logistic regression models, D-dimers above 1128 ng/mL at admission were also associated to a worth prognosis with a OR of 3.07 (95% CI 2.05–4.69, $p < 0.001$) and an unadjusted hazard ratio of 2.11 (95%CI 1.31–3.4, $p < 0.01$).

Conclusions: D-dimer level over 1128 ng/mL is a relevant predictive factor for in-hospital mortality in COVID-19 hospitalized patients in medical ward, regardless the occurrence of VTE during hospitalization.

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is associated with various clinical respiratory syndromes, ranging from mild upper airway symptoms to progressive life-threatening viral pneumopathy (1, 2). Patients with severe coronavirus disease 2019 (COVID-19) have progressive hypoxemia inducing need of mechanical ventilatory support. One specific feature of COVID-19 is the induced-vascular disease. Ackermann et al. recently examined the morphologic and molecular features of lungs obtained during autopsy of patients who died from COVID-19 and evidenced abnormal angiogenic process inside lungs, in contrast to lungs from patients who died from influenza or age-matched and uninfected control lungs (3). COVID-19-induced vascular disease is also associated to an increased level of circulating endothelial cells (4). Moreover, plasma biomarkers of endothelial lesion are also predictive factors for future referral to intensive care unit (ICU), reinforcing the hypothesis of a COVID-19-associated vascular injury (5). SARS-CoV-2 virus has been shown to infect blood vessels and induce vascular damage (6) and fibrin deposits in lung but also in kidney has been found in vascular beds.

A high prevalence of venous thromboembolism (VTE), in particular pulmonary embolism (PE) has been observed in hospitalized COVID-19 patients (7–9). However, more than these macrothrombotic events, microvascular thrombosis in the lungs has been reported following autopsies, suggesting acute

respiratory distress syndrome in COVID-19 (10–12). Thrombo-inflammatory process in pulmonary capillary vessels is probably the main actor of microthrombosis in lung capillaries that induces COVID-19-associated coagulopathy (13), characterized by an increase in procoagulant factors such as fibrinogen, together with a strong increase of D-dimers at admission (1, 2, 14). Level of D-dimers at admission has been associated to in-hospital mortality in several studies (1, 14, 15), however the cut-off allowing deciphering patients with favorable and poor outcomes is still a matter of debate.

Using data from a large multicenter French case series, we aimed to identify a D-dimer cut-off at admission that could be a clear independent predictor of in-hospital mortality.

Methods

Study Settings and Population

From February 26 to April 20, 2020, all consecutive adult patients admitted to hospital with a diagnosis of SARS-CoV-2 infection were included in a retrospective multicentric (24 centers) observational study, which was initiated by the French Society of Cardiology (*NCT04344327*) and named the Critical COVID-19 France (CCF) study (9). Following WHO criteria, SARS-CoV-2 infection was determined by positive results from real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of nasal and pharyngeal swabs or lower respiratory tract aspirates (confirmed case) or was determined by typical imaging characteristics on chest computed tomography (CT) when laboratory testing was inconclusive (probable case) (16).

Data Collection and outcome

All data were collected by local investigators in an electronic case-report form via the REDCap software (Research Electronic Data Capture, Vanderbilt University, United States of America) hosted by a secured server from the French Institute of Health and Medical Research at the Paris Cardiovascular Research Centre. Patient baseline information included demographic characteristics, coexisting medical conditions, cardiovascular comorbidities and chronic medications. Clinical parameters and biological findings were recorded at admission. On the chest CT scan, the degree of pulmonary lesions with ground-glass opacities and areas of consolidation was categorized as low/moderate (< 50% involvement) or severe (> 50% involvement). The oral anticoagulation regimen at admission was categorized into two groups: 1) no anticoagulation 2) oral anticoagulant therapy with vitamin K antagonists or direct oral anticoagulants. The occurrence of symptomatic VTE during hospitalization included PE and/or deep vein thrombosis (DVT).

Outcomes

The primary outcome was in-hospital death to assess predictive performance of D-dimer level at admission in COVID-19 patients.

Statistical Analysis

Continuous data were expressed as mean ($\pm$ standard deviation (SD)) and categorical data as proportion. Continuous variables were compared using Mann-Whitney test and categorical variables were compared using Fisher exact test (17). We generated D-dimer level at admission receiver operating characteristic (ROC) curve for in-hospital mortality. We identified the optimal threshold of D-dimer level at admission using the Youden's J statistic. In the univariate analysis, patients were compared according to the optimal threshold of D-dimers at admission. In the multivariable analysis, we used logistic regression to assess the association between the level of D-dimers (as a categorical dependent variable dichotomized according to the optimal threshold) and platelet count, leukocyte count, or in-hospital mortality (18, 19). The model included as covariates: gender, age, cardiovascular comorbidities such as history of high blood pressure, history of malignancy (cancer in remission or active cancer), plasma creatinine level ($\mu\text{mol/L}$), C-reactive protein (mg/L), the degree of pulmonary lesions with ground-glass opacities and areas of consolidation (dichotomized $<$ or $>$ 50%), the use of oral anticoagulant therapy and the occurrence of VTE during hospitalization. Cox proportional hazard (PH) model with length of stay (days) as a time scale was used to investigate the relationships between the level of D-dimers (as a categorical dependent variable dichotomized according to the optimal threshold) and in-hospital mortality. The model was adjusted for the same potential confounders included in the logistic regression model. Kaplan-Meier method was used to represent Cox PH model results according to the level of D-dimers (as a categorical dependent variable dichotomized according to the optimal threshold). We used the log-rank test to compare the survival distributions according to the optimal threshold of D-dimers. We performed two sensitivity analysis: 1) to take into account the retrospective design and to avoid the bias due to censored data ($n = 268/1154$ (23.2%)), we performed the same multivariable analysis in the population of patients who were discharged alive from hospital or dead in hospital (total patients analyzed $n = 886/1154$ (76.8%)) and thus excluded patient with censored outcome. 2) We performed the D-dimer level at admission ROC curve only in the subgroup of patients with VTE during hospitalization ($n = 127$). We compared the area under the curve (AUC) of the two ROC curves using the Delong's test.

All analyses were 2-sided and a p -value < 0.05 was considered statistically significant. Statistical analysis was performed using R studio software (R Development Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

Results

Optimal D-dimer cut-off predicting in-hospital mortality did not differ in patients with or without VTE during hospitalization

During the study period, a total of 2,878 consecutive patients who were hospitalized in medical ward for SARS-CoV-2 infection were included. At admission, 1154/2878 (40.1%) patients had a mean (SD) age of 64.35 (16.63), and 59.8% (690/1154) were female (Table 1). The optimum cut-off value for D-dimers at admission to predict in-hospital mortality was 1128 ng/mL according to ROC curve (Fig. 1) with a

sensitivity of 71.1% (95% CI 0.62–0.78) and a specificity of 55.6% (95% CI 0.52–0.58), a positive predictive value of 15.8% (95% CI 0.13–0.19) and a negative predictive value of 94.3% (95% CI 0.92–0.96). AUC for in-hospital mortality was 64.9% (95% CI 0.60–0.69). Listed in Table 1 are the initial clinical, biological and radiological characteristics and outcomes of the patients above and beyond the D-dimer cut-off of 1128 ng/mL. At admission, 52.8% (609/1154) patients had D-dimer levels below 1128 ng/mL and 47.2% (545/1154) over 1128 ng/mL. Compared with patients with D-dimer levels below 1128 ng/mL, patients with D-dimer levels $\geq$ 1128 ng/mL were older, had more high blood pressure and chronic kidney disease. Those patients had higher level of creatinine, C-reactive protein, fibrinogen, platelet and leukocyte counts, and a higher rate of severe parenchymal involvement on chest CT-scan. Moreover, those patients had a lower hemoglobin level and PT ratio. The in-hospital mortality rate (15.8% vs 5.7%) and the mean duration of hospitalization (10.25 days (6.47) vs 8.75 days (5.83)) were significantly higher for COVID-19 patients with D-dimer level $\geq$ 1128 ng/mL at admission (Table 1).

Table 1

Clinical, biological and radiological characteristics and outcomes according to optimal threshold of D-dimers at admission ($<$ or $\geq$ 1128 ng/mL).

	Overall population	D-dimers $<$ 1128 ng/mL	D-dimers $\geq$ 1128 ng/mL	p-value
	n = 1154	n = 609	n = 545	
Age, mean (SD)	64.35(16.63)	61.02(15.97)	68.06(16.59)	$<$ 0.001
Age range, n(%)				
(0,50]	232(20.1)	153(25.1)	79(14.5)	$<$ 0.001
(50,60]	210(18.2)	137(22.5)	73(13.4)	
(60,70]	263(22.8)	133(21.8)	130(23.9)	
(70,80]	224(19.4)	106(17.4)	118(21.7)	
(80,90]	157(13.6)	61(10.0)	96(17.6)	
(90,110]	65(5.6)	17(2.8)	48(8.8)	
Male gender, n(%)	690(59.8)	348(57.1)	342(62.8)	0.060
Body Mass Index, mean (SD)	28.24(6.21)	28.46(5.76)	28.00(6.67)	0.240
BMI range, n(%)				
(0,25]	313(27.1)	149(24.5)	164(30.1)	0.195
(25,30]	349(30.2)	193(31.7)	156(28.6)	
(30,66]	320(27.7)	174(28.6)	146(26.8)	
Time from illness onset to hospitalization in days, mean (SD)	7.12(4.76)	7.14(4.61)	7.10(4.92)	0.902
Comorbidities				
High blood pressure, n(%)	557(48.3)	254(41.7)	303(55.6)	$<$ 0.001
Diabetes, n(%)	259(22.4)	126(20.7)	133(24.4)	0.316
Dyslipidemia, n(%)	314(27.2)	152(25.0)	162(29.7)	0.075
History of stroke, n(%)	91(7.9)	46(7.6)	45(8.3)	0.351
Chronic kidney disease, n(%)	150(13.0)	59(9.7)	91(16.7)	$<$ 0.001

	Overall population	D-dimers < 1128 ng/mL	D-dimers ≥ 1128 ng/mL	p-value
Malignancy, n(%)				
No cancer	987(85.5)	544(89.3)	443(81.3)	< 0.001
Cancer in remission	97(8.4)	40(6.6)	57(10.5)	
Active cancer	70(6.1)	25(4.1)	45(8.3)	
Current smoker, n(%)	155(13.4)	82(13.5)	73(13.4)	0.794
Atrial fibrillation, n(%)	129(11.2)	71(11.7)	58(10.6)	0.855
Type of anticoagulation used at admission, n(%)				
no anticoagulation	1025(88.8)	539(88.5)	486(89.2)	0.978
DOACs	74(6.4)	40(6.6)	34(6.2)	
Vitamin K antagonist	50(4.3)	27(4.4)	23(4.2)	
Unfractionated Heparin	5(0.4)	3(0.5)	2(0.4)	
Use of oral anticoagulation (DOACs or VKA), n(%)				
yes	124(10.7)	67(11.0)	57(10.5)	0.906
no	1025(88.8)	539(88.5)	486(89.2)	
In hospital exploration				
Hemoglobin, g/dL, mean (SD)	13.21(1.96)	13.57(1.75)	12.80(2.10)	< 0.001
Platelets, 10 ⁹ /L, mean (SD)	222.46(100.28)	208.34(80.98)	238.31(116.31)	< 0.001
Creatinine level plasma, micromol/L, mean (SD)	98.61(99.85)	87.87(79.77)	110.60(117.22)	< 0.001
Aspartate aminotransferase, UI/L, mean (SD)	56.18(83.32)	51.53(64.91)	61.37(99.74)	0.050
Leukocytes, 10 ⁹ /L, mean (SD)	7.54(5.98)	6.61(3.24)	8.58(7.89)	< 0.001
Lymphocytes, 10 ⁹ /L, mean (SD)	1.31(3.76)	1.21(1.30)	1.41(5.31)	0.370
C-reactive protein, mg/L, mean (SD)	91.52(76.14)	74.57(68.24)	110.40(80.00)	< 0.001

	Overall population	D-dimers < 1128 ng/mL	D-dimers ≥ 1128 ng/mL	p-value
Fibrinogen, g/L, mean (SD)	6.00(1.66)	5.76(1.57)	6.24(1.71)	< 0.001
Ferritin, microg/L, mean (SD)	1063.80(1508.13)	1000.28(1504.82)	1121.25(1512.83)	0.449
PT ratio (%), mean (SD)	85.47(18.16)	87.40(18.67)	83.36(17.37)	< 0.001
aPTT ratio, mean (SD)	1.15(0.31)	1.15(0.32)	1.15(0.30)	0.864
Abnormalities on chest CT, n(%)				
Parenchymal involvement low or moderate (< 50%)	762(66.0)	436(71.6)	326(59.8)	< 0.001
Parenchymal involvement severe (> 50%)	201(17.4)	80(13.1)	121(22.2)	
No chest CT-scan	191(16.6)	93(15.3)	98(18.0)	
Outcomes				
Duration of stay, mean (SD)	9.36(6.14)	8.75(5.83)	10.25(6.47)	0.001
Time from admission to in-hospital death, mean (SD)	15.22(10.29)	16.6(7.82)	13.7(9.19)	0.001
In-hospital death, n(%)	121(10.5)	35(5.7)	86(15.8)	< 0.001

We also evaluated D-dimer level at admission in the subgroup of patients who developed VTE during hospitalization (n = 127). In this subgroup, the optimum cutoff value for D-dimers at admission to predict in-hospital mortality was 1202 ng/mL using ROC curve (Fig. 1) with a sensitivity of 61% (95% CI 0.17–0.92) and a specificity of 25.3% (95% CI 0.12–0.58), a positive predictive value of 5.8% (95% CI 0.01–0.16) and a negative predictive value of 95.3% (95% CI 0.84–0.98). AUC for in-hospital mortality was 63.7% (95% CI: 0.37–0.90). This cutoff value at 1202 ng/mL did not significantly differ from that of the whole study population (p = 0.92).

Increased D-dimer level at admission is an independent predictor of COVID-19 in-hospital mortality

Kaplan-Meier survival curves for D-dimer level showed that level ≥ 1128 ng/mL at admission was a significant predictor of in hospital mortality (p < 0.001, Fig. 2A). Statistical significance of separation

between two groups was achieved at 9 days. As shown in Table 2, D-dimer level ≥ 1128 ng/mL was significantly associated with higher in-hospital mortality (OR 2.08, 95% CI 1.24–3.54, $p = 0.006$) in the logistic regression. In the same way Cox proportional hazard analysis showed that D-dimer level ≥ 1128 ng/ml at admission was also a significant determinant for worst prognosis (HR 2.11 95% CI 1.31–3.4, $p < 0.01$) after adjustment (Fig. 3). In the sensitivity analysis, the D-dimer level at admission ROC curve for in-hospital mortality in the subgroup of patient with VTE during hospitalization ($n = 127$) was similar (Fig. 1b). Moreover, when the analysis was restricted to patients without censored outcome ($n = 886$) the level of association between D-dimer level ≥ 1128 ng/mL and in-hospital mortality remained similar with an OR of 1.88 (95% CI 1.08–3.31, $p = 0.02$) and HR of 2.2 (95% CI 1.25–3.3; $p < 0.01$) (Table 3).

Table 2a

Association between D-dimers cutoff of 1128 ng/mL and in-hospital mortality using logistic regression. OR = Odds Ratio; CI = Confident Interval; DOACs = Direct Oral Anticoagulants, VKA = Vitamin K antagonist, SD = Standard Deviation, CT = Computerized Tomography. *Venous thrombosis event included deep vein thrombosis and Pulmonary Embolism.

	Alive	in-hospital death	OR (univariable)	OR (multivariable)
D-dimers > 1128 ng/mL	459 (44.4)	86 (71.1)	3.07 (2.05–4.69, p < 0.001)	2.08 (1.24–3.54, p = 0.006)
Age				
(50,60]	467 (18.6)	15 (4.2)	1.90 (0.82–4.75, p = 0.149)	0.96 (0.28–3.19, p = 0.943)
(60,70]	577 (23.0)	45 (12.5)	4.60 (2.27–10.63, p < 0.001)	0.88 (0.28–2.84, p = 0.824)
(70,80]	498 (19.8)	77 (21.4)	9.12 (4.63–20.70, p < 0.001)	3.49 (1.40–9.99, p = 0.011)
(80,90]	361 (14.4)	135 (37.5)	22.06 (11.38–49.57, p < 0.001)	9.74 (3.81–28.59, p < 0.001)
(90,110]	138 (5.5)	80 (22.2)	34.20 (17.12–78.40, p < 0.001)	14.94 (5.23–47.60, p < 0.001)
Cancer				
Cancer in remission	183 (7.3)	43 (11.9)	1.87 (1.30–2.64, p = 0.001)	0.80 (0.33–1.76, p = 0.598)
Active cancer	146 (5.8)	43 (11.9)	2.34 (1.61–3.34, p < 0.001)	1.84 (0.77–4.11, p = 0.149)
High blood pressure	1191 (47.6)	262 (73.0)	2.97 (2.33–3.81, p < 0.001)	0.97 (0.56–1.69, p = 0.918)
Oral anticoagulation (DOACs or VKA)	298 (12.0)	84 (23.5)	2.26 (1.72–2.96, p < 0.001)	1.08 (0.53–2.10, p = 0.818)
Plasma creatinine level - μ mol/L, mean (SD)	92.3 (86.4)	139.6 (137.5)	1.00 (1.00–1.00, p < 0.001)	1.00 (1.00–1.00, p = 0.001)
Parenchymal opacification in chest CT-scan > 50%	356 (17.8)	74 (30.0)	1.98 (1.46–2.64, p < 0.001)	2.00 (1.16–3.42, p = 0.012)
Venous thrombosis event*	116 (4.6)	11 (3.0)	0.65 (0.33–1.17, p = 0.180)	0.72 (0.20–1.98, p = 0.562)

Table 2b

b. Association between D-dimers cutoff of 1128 ng/mL and in-hospital mortality using logistic regression in the selected population of patient without censored outcome. OR = Odds Ratio; CI = Confident Interval; DOACs = Direct Oral Anticoagulants, VKA = Vitamin K antagonist, SD = Standard Deviation, CT = Computerized Tomography. *Venous thrombosis event included deep vein thrombosis and Pulmonary Embolism.

	Alive	in-hospital death	OR (univariable)	OR (multivariable)
D-dimers > 1128 ng/mL	313 (40.9)	86 (71.1)	3.55 (2.35–5.45, p < 0.001)	1.88 (1.08–3.30, p = 0.026)
Age				
(50,60]	157 (20.5)	7 (5.8)	1.23 (0.41–3.66, p = 0.705)	1.07 (0.32–3.61, p = 0.909)
(60,70]	168 (22.0)	19 (15.8)	3.12 (1.33–8.15, p = 0.012)	1.03 (0.32–3.41, p = 0.953)
(70,80]	133 (17.4)	25 (20.8)	5.18 (2.29–13.30, p < 0.001)	4.47 (1.73–13.17, p = 0.003)
(80,90]	86 (11.3)	40 (33.3)	12.82 (5.86–32.33, p < 0.001)	9.70 (3.66–29.38, p < 0.001)
(90,110]	27 (3.5)	22 (18.3)	22.47 (9.17–61.57, p < 0.001)	18.04 (5.78–62.28, p < 0.001)
Cancer				
Cancer in remission	67 (8.8)	12 (9.9)	1.25 (0.62–2.31, p = 0.505)	0.80 (0.32–1.84, p = 0.622)
Active cancer	36 (4.7)	14 (11.6)	2.71 (1.37–5.11, p = 0.003)	2.80 (1.06–6.99, p = 0.031)
High blood pressure	333 (43.8)	80 (66.7)	2.56 (1.72–3.88, p < 0.001)	0.92 (0.51–1.64, p = 0.767)
Oral anticoagulation (DOA or VKA)	64 (8.4)	23 (19.0)	2.56 (1.50–4.26, p < 0.001)	1.46 (0.68–3.01, p = 0.320)
Plasma creatinine level - μmol/L, mean (SD)	86.6 (63.0)	139.2 (135.4)	1.01 (1.00–1.01, p < 0.001)	1.01 (1.00–1.01, p < 0.001)
Parenchymal opacification in chest CT-scan > 50%	98 (15.0)	30 (32.6)	2.74 (1.67–4.42, p < 0.001)	3.01 (1.64–5.49, p < 0.001)
Venous thrombosis event*	43 (5.6)	5 (4.1)	0.72 (0.25–1.70, p = 0.503)	1.05 (0.29–3.07, p = 0.929)

Table 3

Association between D-dimer cutoff of 1128 ng/mL and in-hospital mortality using logistic regression in the selected population of patients without censored outcome.

	Alive	in-hospital death	OR (univariable)	OR (multivariable)
D-dimers > 1128 ng/mL	459 (44.4)	86 (71.1)	3.07 (2.05–4.69, p < 0.001)	2.08 (1.24–3.54, p = 0.006)
Age				
(50,60]	467 (18.6)	15 (4.2)	1.90 (0.82–4.75, p = 0.149)	0.96 (0.28–3.19, p = 0.943)
(60,70]	577 (23.0)	45 (12.5)	4.60 (2.27–10.63, p < 0.001)	0.88 (0.28–2.84, p = 0.824)
(70,80]	498 (19.8)	77 (21.4)	9.12 (4.63–20.70, p < 0.001)	3.49 (1.40–9.99, p = 0.011)
(80,90]	361 (14.4)	135 (37.5)	22.06 (11.38–49.57, p < 0.001)	9.74 (3.81–28.59, p < 0.001)
(90,110]	138 (5.5)	80 (22.2)	34.20 (17.12–78.40, p < 0.001)	14.94 (5.23–47.60, p < 0.001)
Cancer in remission	183 (7.3)	43 (11.9)	1.87 (1.30–2.64, p = 0.001)	0.80 (0.33–1.76, p = 0.598)
Active cancer	146 (5.8)	43 (11.9)	2.34 (1.61–3.34, p < 0.001)	1.84 (0.77–4.11, p = 0.149)
High blood pressure	1191 (47.6)	262 (73.0)	2.97 (2.33–3.81, p < 0.001)	0.97 (0.56–1.69, p = 0.918)
Oral anticoagulation (DOACs or VKA)	298 (12.0)	84 (23.5)	2.26 (1.72–2.96, p < 0.001)	1.08 (0.53–2.10, p = 0.818)
Plasma creatinine level - μmol/L, mean (SD)	92.3 (86.4)	139.6 (137.5)	1.00 (1.00–1.00, p < 0.001)	1.00 (1.00–1.00, p = 0.001)
Parenchymal opacification in chest CT-scan > 50%	356 (17.8)	74 (30.0)	1.98 (1.46–2.64, p < 0.001)	2.00 (1.16–3.42, p = 0.012)
Venous thrombosis event	116 (4.6)	11 (3.0)	0.65 (0.33–1.17, p = 0.180)	0.72 (0.20–1.98, p = 0.562)
OR = Odds Ratio; CI = Confidence Interval; DOACs = Direct Oral Anticoagulants, VKA = Vitamin K antagonist, SD = Standard Deviation, CT = Computerized Tomography. *Venous thrombosis event included deep vein thrombosis and Pulmonary Embolism.				

Discussion

The main finding of this retrospective study is that D-dimer level at admission above 1128 ng/mL is an independent predictor of in-hospital mortality for COVID-19 patients. This multicenter French study of patients hospitalized for COVID-19 is the current largest non-monocentric study to date for hospitalized patients in medical ward to provide evidence that initial D-dimer levels could be a valuable tool to predict further in-hospital mortality. Moreover, to the best of our knowledge, we show for the first time that VTE occurrence during hospitalization did not interfere with the predictive value of D-dimers for in-hospital mortality.

High D-dimer level has been largely reported to be one of the most common laboratory findings reported in COVID-19 patients at hospital admission. We previously demonstrated that D-dimer measurement at admission is a discriminant factor during COVID-19 suspicion. Indeed, adding a D-dimer cut-off beyond 500 ng/mL to female gender and absence of pneumonia at CT scan could exclude COVID-19 diagnosis with a high sensitivity and specificity (4). Moreover, we and others previously showed that D-dimer level at admission was higher in patients needing ICU referral compared to those who did not require it (5, 20). Moreover, several reports have described that increased D-dimer levels were related to in-hospital mortality (14, 21–23). Only one study provided a well evaluated cutoff for D-dimers (15) at 2000 ng/mL for relation with in hospital mortality in 343 patients. However, this study did not specify if patients were hospitalized in medical ward, in ICU or if patients were directly hospitalized in ICU, making proper and accurate use of this cut-off difficult for clinicians. Our study only included COVID-19 patients admitted in medical ward. Some of them were secondary referred to ICU but no one was directly hospitalized in ICU. Our results propose COVID-19-increased D-dimer level as a clear consequence of respiratory disease through the development of capillary microthrombosis, as observed in post-mortem studies (3, 11) and attributed to a vascular thickening or vascular congestion (24). Thus, in COVID-19, hypothesis of microthrombosis is proposed in lung but also in kidney since the elevation of serum creatinine was associated with higher levels of D-dimers (> 500 ng/mL) (25). The SARS-CoV-2 receptor (ACE2) is strongly expressed in endothelial cells (26). Infection of endothelial cells could therefore induce endothelial lesions triggering massive activation of coagulation and diffuse microthrombotic process impairing renal function and respiratory gas exchanges. We previously described increased numbers of circulating endothelial cells in COVID-19 patients (4) and an association between circulating biomarkers of endothelial activation in COVID-19 and ICU admission (5). Angiopoietin-2 was also inversely correlated to respiratory system compliance in this study, paving the way of relationship between endothelial dysfunction and pulmonary disease severity. Integrity of endothelial cells allows providing an antithrombotic environment that is reversed during COVID-19 upon the burst of inflammation related to IL-6. Therefore, SARS-CoV-2 infection induces a disruption of endothelial thrombo-protective barrier that lead to this coagulopathy and increased D-dimers. Since in the present cohort, patients were in the same step of disease according to same time to onset symptoms of disease, endothelial induced coagulopathy reflected by D-dimers could be a consequence of viral loading phase and severity of viral infection.

Importance in viral loading hypothesis needs to be confirmed with association between D-dimers and viremia quantified with sensitive tests.

Major confounding factor for D-dimers increase could be macrothrombosis since high incidence of VTE (PE or DVT) (7, 9, 27) have been described in COVID-19. In clinical practice, D-dimer measurements have been used only to exclude VTE. Indeed, no such D-dimer-based strategy has been described during COVID-19-associated coagulopathy with patients with a high level of D-dimers. Even if increased D-dimer levels at admission have been associated with VTE during follow-up in COVID-19 patients (28), no threshold is currently available to diagnose VTE. Furthermore, the International Society of thrombosis and Haemostasis (ISTH) does not recommend routine screening for VTE based on elevated D-dimer levels in COVID-19 patients (29). We demonstrate here that 1128 ng/mL D-dimer cut-off at admission is independently correlated to in-hospital mortality regardless VTE occurrence during hospitalization. D-dimers might be used to monitor COVID-19 worsening. Indeed, previous studies have observed that progressive increase of D-dimers was observed in non-survivors of COVID-19 (1). Microthrombosis generating D-dimers allow to make prognosis in COVID-19 outcome and also opens the way of D-dimer monitoring to guide whether anticoagulation therapy should be initiated in COVID-19. D-dimer monitoring has been described in a randomized clinical trial in patients with mechanical valve replacement as a good tool to guide anticoagulation intensity in patients receiving warfarin therapy (30) but also to determine the duration of oral anticoagulation in patients with VTE (31). Thus, our results suggest that therapeutic anticoagulation could be initiated in COVID-19 patients with high D-dimer level at admission in contrast to patients with D-dimers beyond this cut-off that should only benefit from prophylactic anticoagulation. Moreover, D-dimer-based strategy to guide anticoagulation regimen needs to be evaluated in prospective randomized clinical trials.

Our study has several limitations. First, in this multicentric study, we could not identify the manufacturer or type of D-dimer assay used for all tested D-dimers as suggested by ISTH (32). Second, we do not have the delay from COVID-19 admission to VTE onset during hospitalization. Third, serial D-dimer monitoring has been suggested by ISTH (32) as helpful in determining prognosis in COVID-19 patients. Indeed, a peak of D-dimers has been found associated with VTE in COVID-19 (33, 34) but in the present study, we only assessed D-dimers at admission. However, since VTE occurrence did not modify in-hospital mortality in the present study, this lack of continuous monitoring of D-dimers is unlikely to modify results.

Conclusion

In conclusion, this multicentric retrospective study suggests that D-dimer level at admission could be a valuable biomarker to predict mortality related to COVID-19, independently of VTE occurrence during hospitalization. The determined cut-off at 1128 ng/mL could be a valuable tool to guide anticoagulation intensity in COVID-19 patients. Further prospective studies are necessary to confirm this threshold of D-dimers reflecting COVID-19 worsening.

Abbreviations

95% CI = 95% Confident interval

ACE2 = Angiotensin-converting enzyme 2 SARS-CoV-2 receptor

CCF = Critical COVID-19 France

COVID-19 = Coronavirus disease 2019

CT = Computed tomography

DVT = Deep Veneous Thrombosis

ICU = Intensive care unit

ISTH = International Society of thrombosis and Haemostasis

OR = Odds ratio

PE = Pulmonary embolism

PH = Proportional hazard

PT = Prothrombin

ROC = Receiver operating characteristic

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

SD = Standard deviation

VTE = Venous thromboembolism

Declarations

Ethics approval and consent to participate

The CCF study was declared and authorized by the French data protection committee (authorization no. 2207326v0) and conducted in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments (*NCT04344327*).

Consent for publication

Not applicable

Availability of data and material

Please contact author for data requests

Competing interests

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Authors' contributions

All the undersigning authors have substantially contributed to the paper. David Smadja and Richard Chocron designed the present study and wrote the manuscript. Richard Chocron performed statistical analyses. Ariel Cohen and Guillaume Bonnet designed the trial.

All authors declare that the submitted work is original and has not been published before (neither in English nor in any other language) and that the work is not under consideration for publication elsewhere.

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Figures

	<u>D-dimers</u> Cut-off of 1128 ng/ml	CI 95%
<u>Sensitivity</u>	71.1%	0.62-0.78
<u>Specificity</u>	55.6%	0.52-0.58
PPV	15.8%	0.13-0.19
NPV	94.3%	0.92-0.96

Figure 1

D-dimers level at admission receiver operating characteristic (ROC) curve for in-hospital mortality. (ng/ml). AUC=64.9% (60%-69.7%). The D-dimers level at admission of >1128 ng/mL represents optimal threshold using the Youden’s J statistic. PPV= Positive predictive value; NPV= Negative predictive value; CI 95%= 95% Confidence interval.

Figure 3

a. Forest plot of cox proportional hazard model for in-hospital mortality. HR= Hazard Ratio; CI=Confident Interval; DOACs=Direct Oral Anticoagulants, VKA=Vitamin K antagonist, SD=Standard Deviation, CT= Computerized Tomography. *Venous thrombosis event included deep vein thrombosis and Pulmonary Embolism. b. Forest plot of cox proportional hazard model for in-hospital mortality in the population without censored outcome (n=886). HR= Hazard Ratio; CI=Confident Interval; DOACs=Direct Oral

Anticoagulants, VKA=Vitamin K antagonist, SD=Standard Deviation, CT= Computerized Tomography.

*Venous thrombosis event included deep vein thrombosis and Pulmonary Embolism.