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1 Article

2 Development of a decision support tool for anticoagulation in 3 critically ill patients admitted for SARS-CoV-2 infection: The 4 CALT protocol

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23 **Abstract:** Severe COVID-19 infections are at high risk of thrombo-embolic events (TEE). However, usual exams may be unavailable or unreliable-to predict the risk of TEE at admission or during hospitalization.

24 We performed a retrospective analysis in two centers (n = 124 patients), including severe COVID-19 patients to determine specific risk factors of TEE in SARS Cov2 infection at admission and during the stay in ICU. We used stepwise prediction to create two composite scores in order to predict TEE in the first 48h (H0-H48) and during the first 15 days (D1-D15) in ICU. We then evaluated the performances of our scores in our cohort.

25 During the period H0-H48, patients with a diagnosis of TEE had higher D-Dimers and ferritin values at D1 and day 3 (D3), and a greater drop in fibrinogen between D1 and D3, compared with patients without TEE. Over the period D1-D15, patients with a diagnosis of TEE showed a more marked drop in fibrinogen and had higher D-Dimers and LDH values at D1 and D3. The CALT 1 score, calculated at D1, had a diagnostic performance for TEE at H0-H48 estimated by an AUC of 0.85 (CI95%: 0.76-0.93, p < 10⁻³). The CALT 2 score, calculated at D3, predicted the occurrence of TEE over the period D1-D15 with an estimated AUC of 0.85 (CI95%: 0.77-0.93, p < 10⁻³). These two scores were used as the basis for the development of the CALT protocol, a tool to assist in the decision of anticoagulation during severe SARS-CoV-2 infections.

26 The CALT scores showed good performances to predict the risk of TEE in severe COVID-19 patients at admission and during ICU stay. They could therefore be used in a help-for-decision protocol in order to initiate or no anticoagulation.

27 **Keywords:** COVID-19; pulmonary embolism; immunothrombosis; prediction score ; anticoagulation

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1. Introduction

SARS-CoV-2 infection has been proved to be an important risk factor for the occurrence of thrombo-embolic events (TEE), especially in patients admitted in intensive care units (ICU) [1]. The ability to detect high-risk thrombotic situations in COVID-19 is of major interest. First of all, because of the frequency of TEE in the severe forms of this disease. Secondly, because the current data do not allow us to confirm the interest of systematic curative anticoagulation in these patients. Thus, several clinical trials have shown that although a curative anticoagulation protocol allowed a reduction in the occurrence of TEEs compared with a conventional strategy, it had no impact on mortality or the occurrence of organ failure. Moreover, the introduction of curative anticoagulation was associated in these studies with a significant increase in the risk of bleeding events [2]. These data thus underline the importance of individualizing the assessment of thrombotic risk leading to the initiation of curative anticoagulation in severe COVID-19.

Various studies have tried to understand the specificity of TEE in COVID-19 patients and it quickly appeared that coagulopathy resulting from SARS-CoV-2 infections is intimately linked with immunity activation in a phenomenon of immunothrombosis [3]. This finding is paralleled by a change in the biological profile of patients, as an increase in D-Dimers and fibrinogen [4].

The description of this phenomenon leads to interrogations about the accuracy of usual thrombo-embolism markers as D-Dimers which have often proven higher in SARS Cov2 infection [5]. Moreover, morphological exams are not always available for critical COVID-19 patients due to precarious respiratory status or acute kidney injury [6]. There is consequently a challenge to diagnose and to predict the occurrence of TEE either at admission and later during the ICU stay. Considering the physiopathology of immunothrombosis, various studies tried to link the usuals thrombo-embolic markers to the occurrence of TEE [7] but, in our knowledge, none of them focused on COVID-related immune markers.

In this retrospective study, we aimed to develop the CALT protocol, based on usual clinical variables and on routinely available biomarkers for the prediction of TEE in critically ill patients with severe COVID-19 infection.

2. Materials and Methods

2.1 Study population

We retrospectively included patients hospitalized in medical ICU from two French hospitals (CHU de Lille and Hôpital Foch, Suresnes, France) between September 2020 and March 2022. Included patients met the following criteria: age over 18, admission in ICU for a COVID-19 infection confirmed with RT-PCR, need for a ventilatory support, endocan dosage, thoracic CT-scan with injection in the first 48h of ICU stay (H0-H48) in order to diagnose a potential pulmonary embolism (PE). Patients with a positive RT-PCR at admission but with an alternative etiology to respiratory distress were not included in the study.

2.2 Data collection and definitions

Patient demographic characteristics and comorbidities were recorded, as well as the occurrence of a TEE, defined by a diagnosis of PE confirmed by thoracic CT-scan or a diagnosis of deep veinous thrombosis (DVT) confirmed by venous echo Doppler. We defined the day of admission to the ICU (D1) as the first day of hospitalization in the ICU of one of the two centers of the study. Further data about the infection (vaccinal status, PE or DVT at admission, variant) and about the therapeutics initiated in the first 48 hours and during the ICU stay were also recorded. Blood samples were collected at baseline and at day 3 (D3). In accordance with the French law, no written consent was required for this retrospective study.

2.3 Statistical analysis

2.3.1 Exploratory analysis

Categorical variables were expressed as numbers (percentages). Normally distributed continuous variables were expressed as means (SD). Non-normally distributed variables were expressed as median (IQR). Normality of distribution was checked graphically and by using the Shapiro-Wilk test. The association between two variables was evaluated with a bivariate analysis.

2.3.2 Data imputation

We performed a missing value imputation for continuous variables in the derivation cohort using the predictive mean-matching method with the *mice* function in R (*mice* R package) [8]. Counts of missing data for continuous variables are shown in **Table S1**. Variables with missing data exceeding 35% of total count were excluded from the analysis.

2.3.3 Derivation of CALT-1 and CALT-2

Covid-related Acute Lung and deep veinous Thrombosis (CALT)-1 and CALT-2 scores were then constructed by multivariate logistic regression. We included the following explicative variables for the derivation of CALT-1: gender, age, weight, height, body mass index (BMI), admission SAPS 2, admission SOFA, diabetes, antiplatelet drug prior to hospitalization in the ICU, immunosuppression, vaccination status, variant, percentage and type of predominant COVID pulmonary lesions on the admission CT-scan, treatments over the H0-H48 period by high-flow nasal oxygen (HFNO), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), invasive ventilation, extracorporeal membrane oxygenation (ECMO), the following biomarkers measured at D1: CRP, leukocytes, total lymphocytes, ferritin, PCT, fibrinogen, D-Dimers, LDH, endocan.

The CALT-2 score was derived by including the same variables as for the CALT-1 score, as well as the following biomarkers measured at D3 and their respective variations from the values measured at D1: CRP, leukocytes, lymphocytes, fibrinogen, D-Dimers, ferritin, PCT, LDH, endocan. For each score we selected the predictor variables that contribute the most to the model using the stepwise regression method. We assessed the predictive performance of each model by calculating its area under receiver operating characteristics (AUROC). The coefficients assigned to each selected variable were rounded to the nearest integer. We selected the predictor variables that contribute the most to the model using the smallest Akaike information criterion, allowing to maximize the predictive performance while limiting model complexity. All statistical tests were two-tailed, and p-values < 0.05 were considered statistically significant. The statistical analyses were performed using R version 4.1.2 (R foundation for statistical computing, Vienna, Austria).

3. Results

3.1. Patients' characteristics according to the presence or absence of TEE

We compared the clinical characteristics and biomarkers between patients with and without diagnosis of TEE over the periods H0-H48 and D1-D15. The results of this analysis are shown in **Table 1**.

Table 1. Clinical characteristics associated with TEE

	TEE H0-H48		P	TEE D1-D15		P
	No (n = 100)	Yes (n = 24)		No (n = 90)	Yes (n = 34)	
Demographics						
Gender (male), n (%)	68 (68)	17 (71)	0.98	60 (67)	25 (74)	0.60
Age (years), mean (SD)	61 (11)	62 (11)	0.49	61 (11)	61 (11)	1

Comorbidities,						
BMI (kg/m ²), mean (SD)	31 (7)	31 (7)	0.61	32 (7)	30 (6)	0.22
BMI > 30 kg/m ² , n (%)	57 (61)	7 (32)	0.027	52 (62)	12 (38)	0.031
Diabetes, n (%)	42 (42)	4 (17)	0.038	39 (43)	7 (21)	0.033
Chronic respiratory failure, n (%)	7 (7)	0 (0)	0.4	7 (8)	0 (0)	0.22
COPD, n (%)	4 (4)	1 (4)	1	4 (4)	1 (3)	1
Chronic heart failure, n (%)	7 (7)	0 (0)	0.4	7 (8)	0 (0)	0.22
Cirrhosis (Child B or C), n (%)	1 (1)	0 (0)	1	1 (1)	0 (0)	1
End stage kidney disease, n (%)	4 (4)	0 (0)	0.72	4 (4)	1 (3)	0.5
Immunocompromised, n (%)	14 (14)	2 (8)	0.69	14 (16)	2 (6)	0.26
Antiplatelet drug prior to hospitalization, n (%)	22 (27)	0 (0)	0.01	22 (29)	0 (0)	0.001
SAPS 2, mean (SD)	41 (14)	43 (17)	0.45	41 (14)	42 (15)	0.58
SOFA, mean (SD)	5 (4)	6 (4)	0.36	5 (4)	6 (4)	0.28
SARS-CoV-2 infection						
Variant,						
Wild, n (%)	53 (63)	13 (68)		48 (65)	18 (62)	
Alpha, n (%)	16 (19)	5 (26)		14 (19)	7 (24)	
Delta, n (%)	15 (18)	1 (5)	0.36	12 (16)	4 (14)	0.83
Vaccinal status,						
Not vaccinated, n (%)	87 (91)	21 (88)		77 (90)	31 (91)	
Complete scheme, n (%)	2 (2)	0 (0)		2 (2)	0 (0)	
Incomplete scheme, n (%)	7 (7)	3 (13)	0.56	7 (8)	3 (9)	0.67
Symptoms onset - ICU admission (days), mean (SD)	9 (6)	9 (5)	0.97	9 (5)	9 (5)	0.76
Extension of lung injury on CT-scan (%), mean (SD)	52 (21)	57 (20)	0.41	51 (21)	58 (10)	0.16
Predominant findings in CT,						
Consolidation, n (%)	58 (73)	14 (74)		55 (71)	20 (77)	
Ground-glass opacities, n (%)	42 (27)	10 (26)	1	35 (29)	14 (23)	0.71
Treatments during ICU hospitalization						
Corticosteroids, n (%)	83 (83)	19 (80)	0.89	77 (86)	25 (74)	0.19
Remdesivir, n (%)	9 (9)	1 (4)	0.72	2 (2)	1 (3)	1
Tocilizumab, (n%)	2 (2)	1 (4)	1	7 (8)	3 (9)	1
HFNO H0-H48, n (%)	57 (57)	14 (58)	1	52 (58)	19 (56)	1
CPAP H0-H48, n (%)	28 (29)	7 (29)	1	27 (30)	8 (24)	0.62
NIV H0-H48, n (%)	25 (25)	4 (17)	0.55	22 (24)	7 (21)	0.83
IV H0-H48, n (%)	50 (50)	12 (50)	1	45 (50)	17 (50)	1
ECMO H0-H48, n (%)	12 (12)	6 (25)	0.19	10 (11)	8 (24)	0.14
Prone positioning H0-H48, n (%)	19 (19)	4 (17)	1	16 (18)	7 (21)	0.92
Antibiotherapy H0-H48, n (%)	66 (66)	17 (71)	0.83	59 (65)	24 (71)	0.75
Outcomes						
Duration of mechanical ventilation (days), mean (SD)	14 (15)	17 (20)	0.43	13 (15)	19 (18)	0.063
Duration of antibiotherapy (days), mean (SD)	11 (11)	12 (13)	0.76	10 (11)	13 (12)	0.27
ICU length of stay (days), mean (SD)	19 (18)	21 (22)	0.58	18 (19)	22 (20)	0.3
Mortality at D28, n (%)	34 (34)	4 (17)	0.16	31 (34)	7 (21)	0.2
Mortality at ICU discharge, n (%)	38 (38)	6 (25)	0.34	33 (37)	11 (32)	0.81

Results for quantitative variables are expressed as mean with standard deviation (SD). Qualitative variables are expressed by their number and percentage of the total number of patients excluding missing data. BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, CPAP: Continuous Positive Airway Pressure, ECMO: Extra Corporeal Membrane Oxygenation, NIV: Non-invasive Ventilation, IV: Invasive Ventilation.

One hundred and twenty-four patients were included in our study. Thirty-three (26%) patients were diagnosed with PE either at admission or during the stay in ICU.

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Twenty-three patients (70%) were diagnosed during the H0-H48 period and 10 (30%) were diagnosed between the 3rd and 15th day (D3-D15) of hospitalization in ICU. Two patients in the cohort developed DVT, both diagnosed within the first 48 hours of stay. Forty-four patients (35%) died during their stay in the ICU.

Patients with TEE at H0-H48 had a lower frequency of BMI > 30 kg/m² than patients without TEE at H0-H48 (7 patients (32%) in the TEE group vs. 57 patients (61%) in the no-TEE group, p = 0.027), diabetes (4 patients (17%) in the TEE group vs. 42 patients (42%) in the non-TEE group, p = 0.038) and antiplatelet drug prior to hospitalization in the ICU (no patient (0%) in the TEE group vs. 22 patients (27%) in the non-TEE group, p = 0.01). Furthermore, compared to patients without TEE at D1-D15, patients with TEE at D1-D15 had a lower frequency of BMI > 30 kg/m² (12 patients (38%) in the TEE group vs. 52 patients (62%) in the no-TEE group, p = 0.031), diabetes (7 patients (21%) in the TEE group vs. 39 patients (43%) in the no-TEE group, p = 0.033) and antiplatelet drug prior to hospitalization in the ICU (no patient (0%) in the TEE group vs. 22 patients (29%) in the non-TEE group, p = 0.001).

Table 2. Biomarkers associated with TEE

	TEE H0-H48		p	TEE D1-D15		p
	No (n = 100)	Yes (n = 24)		No (n=90)	Yes (n=34)	
CRP (mg/L), median (IQR)						
D1	133 [68; 186]	156 [81; 211]	0.30	130 [70; 196]	150 [83; 182]	0.48
D3	67 [37;135]	45 [20; 124]	0.47	66 [34; 120]	58 [36; 153]	0.94
Delta	-50 [-125; 21]	-53 [-128; 39]	0.86	-57 [-125; 8]	-48 [-126; 45]	0.52
Leukocytes (G/L), median (IQR)						
D1	9 [5.7; 12]	10.2 [7;14]	0.2	9 [6; 12]	9 [6; 12]	0.22
D3	10 [8; 13]	13 [9; 15]	0.14	11 [8; 13]	11 [8; 13]	0.49
Delta	1 [-1; 5]	2 [-3; 3]	0.71	1 [-1; 5]	1 [-1; 5]	0.27
Lymphocytes (G/L), median (IQR)						
D1	0.6 [0.4; 0.9]	0.6 [0.5; 0.9]	0.66	0.6 [0.4; 0.9]	0.6 [0.5;0.9]	0.49
D3	0.8 [0.5; 1.1]	0.7 [0.4; 1.2]	0.64	0.8 [0.5; 1.1]	0.6 [0.4; 0.9]	0.071
Delta	0 [-0.2; 0.5]	0.2 [0; 0.3]	0.76	0.2 [-0.1; 0.5]	-0.1 [-0.3; 0.2]	0.058
Platelets (G/L), median (IQR)						
D1	237 [193; 308]	254 [201; 319]	0.4	239 [193; 306]	251 [193; 341]	0.45
D3	276 [222; 344]	303 [206; 400]	0.51	278 [218; 350]	270 [213; 378]	0.84
Delta	60 [-9; 103]	31 [-40; 69]	0.26	60 [-9; 105]	22 [-51; 66]	0.07
Fibrinogen (g/L), median (IQR)						
D1	6.8 [5.9; 7.6]	6.3 [5.3; 7.4]	0.32	6.8 [5.8; 7.6]	6.4 [5.7; 7.4]	0.7
D3	5.8 [5.1; 7]	5 [3.7; 5.9]	0.006	5.7 [5; 7]	5.4 [3.9; 6.2]	0.11
Delta	-0.6 [-1.4; -0.1]	-1.7 [-2.3; -0.5]	0.006	-0.6 [-1.4; 0.1]	-1.6 [-2.2; -0.5]	0.02
D-Dimers (µg/L), median (IQR)						
D1	1100 [710; 2450]	2830 [1121; 4054]	0.033	1075 [715; 2293]	1991 [1048; 4000]	0.025
D3	1215 [710;1957]	3590 [1549; 4000]	0.002	1176 [710; 1740]	3795 [1537; 4000]	<0.001
Delta	0 [-575; 392]	-75 [-3089; 1348]	0.77	0 [-566; 360]	-75 [-3089; 1348]	0.81
Ferritin (µg/L), median (IQR)						
D1	1207 [684; 2149]	2304 [1373; 3497]	0.006	1175 [675; 2175]	1692 [1264; 3123]	0.007
D3	1241 [882; 2161]	2434 [1305; 3384]	0.038	1223 [853; 2096]	1468 [1115; 3210]	0.062
Delta	-197 [-787; -24]	284 [-557; 543]	0.12	-227 [-801; -35]	122 [-430; 543]	0.057
LDH (IU/L), median (IQR)						
D1	458 [357; 588]	616 [490; 777]	0.007	458 [356; 587]	616 [470; 769]	0.004
D3	443 [358; 591]	564 [465; 676]	0.084	443 [349; 575]	564 [454; 679]	0.045
Delta	-10 [-64; 66]	-40 [-155; 23]	0.6	-11 [-63; 59]	-21 [-113; 34]	0.67

PCT (ng/mL), median (IQR)						
D1	0.3 [0.1; 1.2]	0.2 [0.1; 0.8]	0.71	0.3 [0.1; 1.2]	0.2 [0.2; 0.7]	0.73
D3	0.2 [0.1; 0.6]	0.2 [0.1; 0.3]	0.48	0.2 [0.1; 0.6]	0.2 [0.1; 0.4]	0.87
Delta	-0.1 [-0.5; 0]	-0.1 [-0.3; 0]	0.74	-0.1 [-0.5; 0]	-0.2 [-0.5; 0]	0.69
Endocan (ng/mL), median (IQR)						
D1	6.7 [4; 13]	4.8 [3.6; 10.2]	0.17	6.7 [4; 14.6]	6 [3; 11]	0.1
D3	7.3 [4; 14]	9.2 [4; 21]	0.28	7 [4.8; 14]	11 [5.4; 20]	0.19
Delta	0.4 [-2; 3]	0.3 [-1.3; 11]	0.59	0 [-3.2; 2.8]	1.8 [-0.2; 7.8]	0.11

The variables are expressed as median and interquartile range (IQR). The difference in value between D1 and D3 is expressed in absolute value. CRP: C-reactive protein, LDH: Lactate dehydrogenase, PCT: Procalcitonin, TEE: Thrombo-embolic event.

The comparison of biological variables according to the presence or absence of TEE over the periods H0-H48 and D1-D15 are shown in **Table 2**. Compared with the group without TEE at H0-H48, there was a significantly higher value in the group with TEE at H0-H48 for D-Dimers at D1 (median (IQR): 2830 (1121; 4054) in the TEE group vs. 1100 (710; 2450) in the no-TEE group, $p = 0.033$), D-Dimers at D3 (median (IQR): 3590 (1549; 4000) in the TEE group vs 1214 (750; 1957) in the no-TEE group, $p = 0.002$), ferritin at D1 (median (IQR): 2304 (1373; 3497) in the TEE group vs. 1207 (684; 2149) in the no-TEE group, $p = 0.006$), ferritin at D3 (median (IQR): 2434 (1305; 3384) in the TEE group vs. 1241 (882; 2161) in the no-TEE group, $p = 0.038$), and LDH at D1 (median (IQR): 616 (490; 777) in the TEE group vs. (458 (357; 588) in the non-TEE group, $p = 0.007$). In addition, in patients with TEE at H0-H48, we found lower fibrinogen at D3 (median (IQR): 5 (3.7; 5.9) in the TEE group vs. 5.8 (5.1; 7) in the no-TEE group, $p = 0.006$) and a greater decrease in fibrinogen between D1 and D3 (median (IQR): -1.7 (-2.3; -0.5) in the TEE group vs. -0.6 (-1.4, -0.1) in the no-TEE group, $p = 0.006$).

Compared with the group without TEE over the period D1-D15, there was a significantly higher value in the group with TEE at D1-D15 for D-Dimers at D1 (median (IQR): 1991 (1048; 4000) in the TEE group vs. 1075 (715; 2293) in the no-TEE group, $p = 0.025$), D-Dimers at D3 (median (IQR): 3795 (1537; 4000) in the TEE group vs. 1176 (710; 1740) in the no-TEE group, $p < 0.001$), LDH at D1 (median (IQR): 616 (470; 769) in the TEE group vs. (458 (356; 587) in the no-TEE group, $p = 0.004$), LDH at D3 (median (IQR): 564 (454; 679) in the TEE group vs. 443 (349; 575) in the no-TEE group, $p = 0.045$) and ferritin at D1 (median (IQR): 1692 (1264; 3123) in the TEE group vs. 1175 (675; 2175) in the no-TEE group, $p = 0.007$). In addition, there was a greater decrease in fibrinogen between D1 and D3 in the TEE group (median (IQR): -1.6 (-2.2; -0.5) in the TEE group vs. -0.6 (-1.4; 0.1) in the non-TEE group, $p = 0.02$).

3.2 Construction of CALT-1 and CALT-2 scores

We then used a bidirectional stepwise logistic regression to construct predictive scores for the diagnosis of TEE in our study population. This method allowed us to develop: 1) the CALT-1 score, calculated at D1, aimed at predicting the existence of a TEE diagnosed during the period H0-H48, and designed as a tool to help in the decision of anticoagulation at D1; 2) the CALT-2 score, calculated at D3, aimed at predicting the existence of a TEE diagnosed during the period D1-D15, and designed as a tool to help in the decision of anticoagulation at D3.

3.2.1 Construction and evaluation of the CALT-1 score

The variables and coefficients used in the construction of CALT-1 are presented in **Figure 1A**.

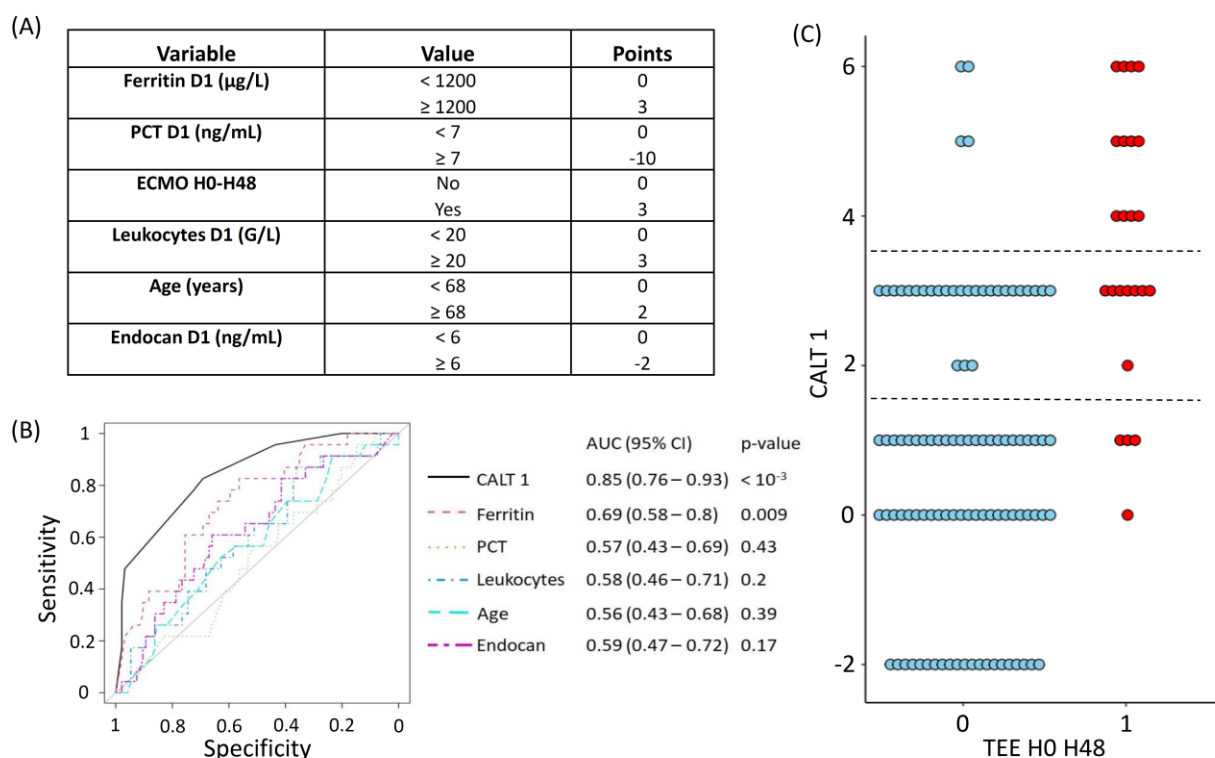


Figure 1. Description and evaluation of the accuracy of the CALT-1 score for the diagnosis of TEE at H0-H48. (A) Variables retained for the construction of the CALT-1 score. (B) ROC curves of the CALT-1 score and of its constitutive variables for the diagnosis of TEE over the H0-H48 period. (C) Values of CALT-1 score according to the presence or absence of TEE at H0-H48. Red dots represent patients with TEE diagnosed in the H0-H48 period. Blue dots represent patients without diagnosis of TEE in the H0-H48 period. The dotted lines represent the low and high decision thresholds used for the CALT-1 score. AUC: Area Under the Curve, CALT: COVID-related Acute Lung and deep venous Thrombosis, ECMO: Extra Corporeal Membrane Oxygenation, TEE: Thrombo-Embolitic Event, PCT: Procalcitonin

The performance of the CALT-1 score was evaluated through its ROC curve, which was compared with those of all the parameters constituting this score. The area under the ROC curve (AUROC) of the CALT-1 score to predict the diagnosis of TEE in the H0-H48 period was calculated at 0.85 (CI95%: 0.76-0.93, $p < 10^{-3}$). In comparison, the best performing single variable was ferritin, whose AUROC curve was calculated at 0.69 (CI95%: 0.58-0.8, $p = 0.009$) (Figure 1B). In addition, the values taken by CALT-1 according to the presence or absence of TEE over the H0-H48 period are shown in Figure 1C and the intrinsic performances of CALT-1 (sensitivity and specificity), as well as the positive (PPV) and negative (NPV) predictive values in our cohort, are described in Table S2. Based on these results, we identified two thresholds of interest for CALT-1 which could be considered in an anticoagulation decision support algorithm. Indeed, we observe that a CALT-1 value strictly lower than 2 was associated with a specificity at 69%, meaning that it correctly identified 69 out of 100 patients without TEE at H0-H48 in our cohort, with a NPV at 95%. Besides, a CALT-1 value greater than or equal to 4 had a sensitivity at 50%, meaning that it was able to detect 12 out of 24 patients with TEE at H0-H48 in our cohort, with a PPV at 74%.

3.2.2 Construction and evaluation of the CALT-2 score

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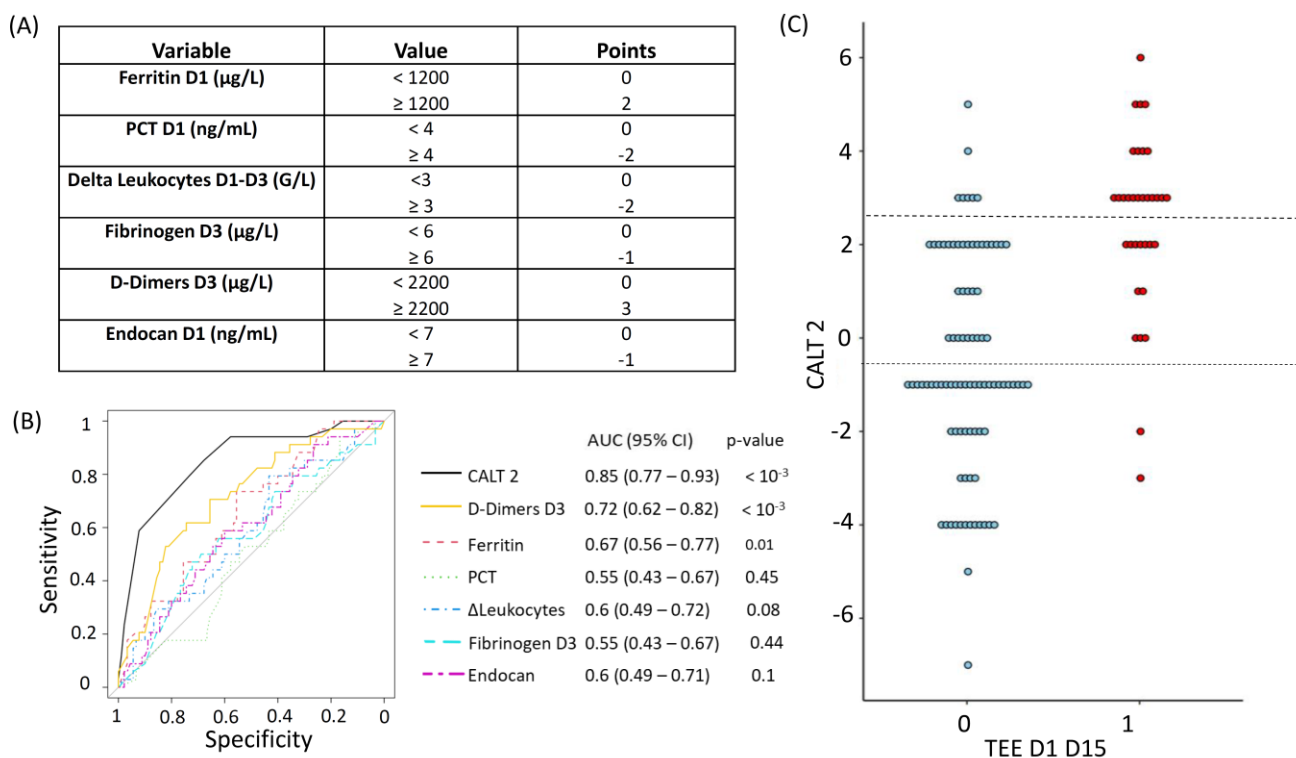


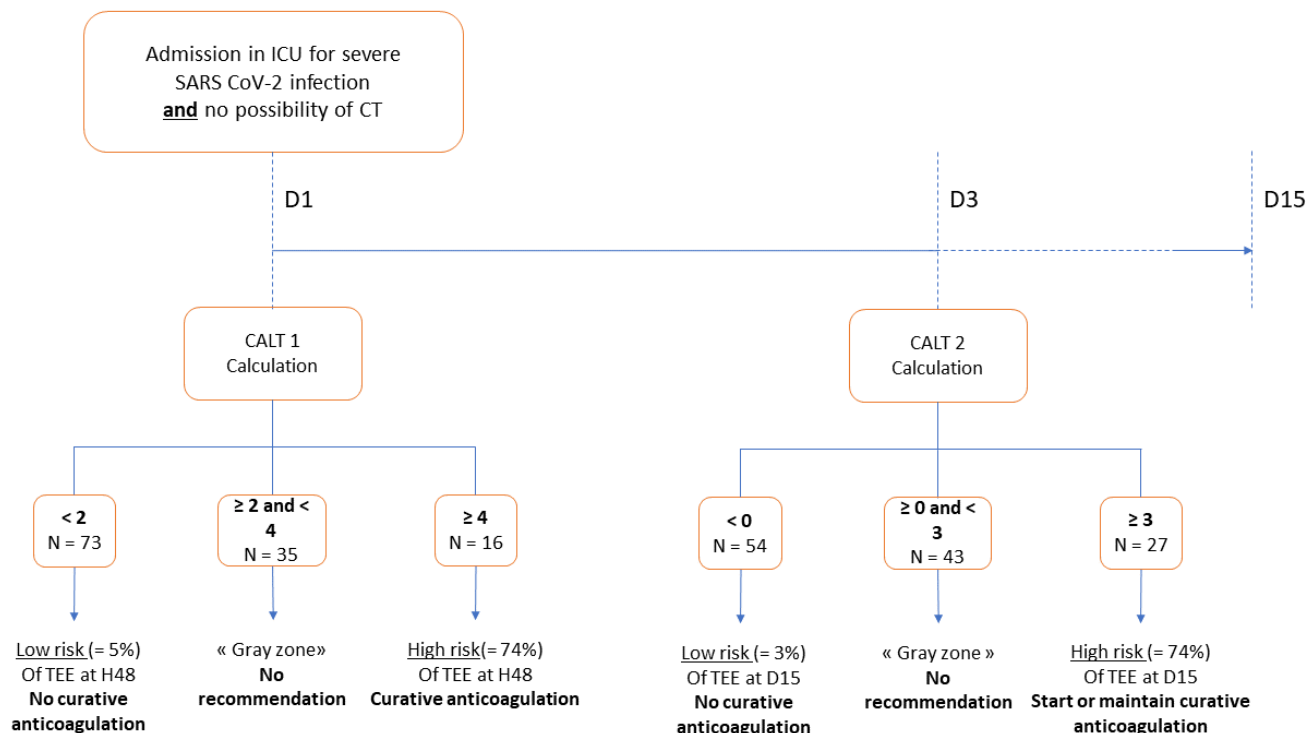
Figure 2. Description and evaluation of the accuracy of the CALT-2 score for the prediction of TEE at D1-D15. (A) Variables retained for the construction of the CALT-2 score. (B) ROC curves of the CALT-2 score and of its constitutive variables for the prediction of TEE over the D1-D15 period. (C) Values of CALT-2 score according to the presence of absence of TEE at D1-D15. Red dots represent patients with TEE diagnosed in the D1-D15 period. Blue dots represent patients without diagnosis of TEE in the D1-D15 period. The dotted lines represent the low and high decision thresholds used for the CALT-2 score. AUC: Area Under the Curve, CALT: COVID-related Acute Lung and deep venous Thrombosis, ECMO: Extra Corporeal Membrane Oxygenation, TEE: Thrombo-Embolitic Event, PCT: Procalcitonin

Concerning the CALT-2 score, the variables and coefficients retained for its construction are shown in **Figure 2A**. As for CALT-1, we evaluated the accuracy of CALT-2 by calculating its AUROC, which we compared with those of its constitutive parameters. The AUROC of CALT-2 to predict the diagnosis of TEE over the period D1-D15 was calculated at 0.85 (CI95%: 0.77-0.93, $p < 10^{-3}$). D-Dimers measured at D3 was identified as the single parameter with the best performances with an AUROC calculated at 0.72 (CI95%: 0.62-0.82, $p < 10^{-3}$) (**Figure 2B**). The values taken by CALT-2 according to the presence or absence of TEE over the period D1-D15 are shown in **Figure 2C**. Sensitivity, specificity, as well as PPV and NPV of CALT-2 in our cohort are shown in **Table S3**.

Similar to the first part of the protocol, we retained two thresholds of clinical interest for the CALT-2 score. A CALT-2 value strictly lower than 0 had a specificity at 58%, meaning it allowed for the detection of 52 out of 90 patients with no diagnosis of TEE at D1-D15, with a NPV at 97%. Additionally, a CALT-2 value greater than or equal to 3 yielded a sensitivity at 59%, meaning it detected 20 out of 34 patients with a diagnosis of TEE at D1-D15, with PPV at 72%.

3.2.3 Proposal of a decision support algorithm for anticoagulation

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Figure 3. Description of the CALT protocol. CALT: COVID-related Acute Lung and deep venous Thrombosis, CT: computed tomography, TEE: Thrombo-Embolic Event

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Based on these results, we propose a decision algorithm, the CALT protocol, described in **Figure 3**. Following this protocol, calculation of the CALT 1 score is performed at D1 and allows to help deciding the initiation of anticoagulation if the score is greater than or equal to 4. If the score is strictly less than 2, the protocol suggests not initiating curative anticoagulation. In the "grey" area between these two thresholds, the protocol does not make any specific suggestion regarding anticoagulation. The protocol then relies on the calculation of the CALT 2 score at D3 to assess the probability of a diagnosis of TEE over the period D1-D15. In case of a CALT 2 score greater than or equal to 3, associated with a high risk of diagnosis of TEE over the period D1-D15, the protocol suggests that curative anticoagulation should be maintained or introduced from D3. In the case of a CALT 2 score strictly below 0, the protocol suggests that curative anticoagulation should not be maintained or introduced. A CALT 2 score between these two limits falls into the "grey zone", for which no recommendation regarding anticoagulation is done.

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4. Discussion

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The identification of predictive markers of TEE appears to be relevant for severe SARS-CoV-2 pneumonia as the use of CT-scan may be compromised by the severity of the patient, possible contra-indications, or the unavailability of the technique. Thus, in a previous study, 30% of patients did not have a CT-scan during their hospitalization in ICU [6]. The main purpose of this study was to propose a practical tool to help the clinician in the decision to start or maintain curative anticoagulation in severe COVID-19. Few studies to our knowledge have investigated markers predictive of TEE in patients admitted to the ICU with SARS-CoV-2 infection. Furthermore, most studies have focused on markers previously evaluated in venous thromboembolic disease. Thus, the

295 interest of D-Dimers has been assessed in several studies, both as a marker of TEE [9]
296 and mortality [5]. However, its lack of specificity make it unreliable as a standalone di-
297 agnostic marker, particularly in the setting of intensive care [10]. Our study identified
298 several factors associated with the risk of TEE in the first 15 days after ICU admission.
299 Concerning the risk of TEE in the H0-H48 period, obesity, diabetes and prior antiplatelet
300 treatment were less frequently found in the group with TEE. Higher D-Dimers values
301 and an inflammatory biological profile on admission (high ferritin and LDH values)
302 were associated with the diagnosis of TEE at H48.

303 The identification of diabetes, obesity and antiplatelet treatments as protective fac-
304 tors was surprising. Indeed, previously published results suggested a positive associa-
305 tion between TEE and obesity [11] or diabetes [12]. However, data are divergent, and
306 other studies did not find a significant association [13]. Besides, the absence of protective
307 effect of antiplatelet treatments to prevent TEE in the setting of severe COVID-19 has
308 been reported in a recent work [14]. Concerning the association between TEE and bio-
309 logical parameters, our study confirmed the predictive character of D-Dimers levels, as
310 demonstrated in previous studies. We also found an association between increased in-
311 flammatory parameters (ferritin, fibrinogen and LDH) and TEE. This correlation be-
312 tween high inflammatory parameters and the occurrence of TEE was consistent with
313 other results reporting an association between incidence of TEE and either higher ferritin
314 [15] or CRP and PNN levels. [16]

315 In order to make the connection between these epidemiological observations and
316 our clinical practice, we have developed a tool to help in the decision of anticoagulation,
317 relying on two scores, CALT 1 and 2, allowing to estimate the thrombo-embolic risk dur-
318 ing the stay in the ICU.

319 The models derived from our logistic regression analyses for CALT 1 and CALT 2
320 scores consistently show an association between elevated inflammatory parameters and
321 the diagnosis of TEE. The leukocyte count and ferritin are thus found in these scores as
322 predictors of the diagnosis of TEE. More unexpectedly, CALT 1 and 2 incorporate ele-
323 vated endocan, previously described as a marker of lung inflammation, as a protective
324 factor. This marker was previously studied in severe COVID as a prognostic marker [6]
325 but to our knowledge it had never been evaluated as a thromboembolic marker in this
326 context. It should be noted that the interest of endocan for the diagnosis of PE outside
327 COVID was suggested in a previous study [10], leading some authors to hypothesize
328 that this association could be found in the context of SARS-CoV-2 infection. However,
329 our study seems to refute this hypothesis. Procalcitonin appears, in our study, to be ne-
330 gatively associated with the risk of TEE. This result can be explained by the predictive
331 value of procalcitonin for bacterial infections [17]. Thus, in case of COVID requiring
332 transfer to the ICU, a high procalcitonin value seems to increase the probability of bacte-
333 rial superinfection, thus decreasing the probability of a thrombo-embolic hypothesis as a
334 cause of the aggravation. Age is also a predictor of TEE at admission in our model,
335 which appears consistent with its status as an important risk factor for venous thrombo-
336 embolic disease both in the general population and in patients infected with SARS-CoV-
337 2 [18]. Several potential benefits of the CALT protocol can be underlined for clinical
338 practice. Firstly, the inclusion of additional explanatory variables appears to provide
339 greater accuracy than the use of each factor individually, as illustrated by the ROC
340 curves presented in our results. In addition, the use of CALT 1 and CALT 2 scores could
341 be useful to guide the decision of anticoagulation in patients admitted to the ICU for
342 SARS-CoV-2 infection, via a two-step strategy. First, CALT 1, calculated at admission to
343 the ICU, could be considered in order to decide whether or not to initiate curative anti-
344 coagulation for the first 48 hours, for patients in whom chest CT-scan cannot be per-
345 formed at ICU admission. This situation seems to concern a non-negligible proportion of
346 patients admitted to the ICU for COVID, as previously described in our center [6]. Al-
347 ternatives to CT-scan have been studied, such as EBUS in patients with ECMO [19] or
348 V/P scintigraphy [18]. However, these techniques remain difficult to access for critically

ill patients and are not widely used in current practice. In a second phase, on the third day of hospitalization, the calculation of CALT 2 seems to allow the identification of patients who should benefit from curative anticoagulation, because of a hypercoagulable state, at high risk of constituted or future thrombosis.

Our study has several strengths. It is a bicentric study covering a large period over several epidemic waves during which practices have evolved. Most of the parameters evaluated are used in common practice. On the other hand, we extended our investigations to factors that are less widely used but of potential interest in view of the pathophysiology of the coagulopathy observed during severe SARS-CoV-2 infection. We also propose a practical algorithm for routine clinical practice based on a two-stage decision score which can be used in patients in whom CT-scan cannot be performed.

One of the main limitations of our study is the absence of data before current hospitalization. We included a heterogeneous population, including subjects coming from home, from conventional hospitalization or from another ICU, most often in order to benefit from ECMO. As such, we could not collect reliable data on the existence of previous thromboprophylaxis or curative anticoagulation. Furthermore, we did not collect data on the prophylactic or curative nature of anticoagulation during the stay. This limitation can be tempered for several reasons. First, anticoagulation is frequently stopped in the ICU, whether for invasive procedures, transport or because of the occurrence of bleeding events. Secondly, a study by Novelli et al. highlights the frequent discrepancy between the target and the level of anti-Xa activity actually achieved during curative anticoagulation [20].

A second limitation concerns the retrospective nature of the study, which resulted in missing data (see **Table S1**). Nevertheless, our score constructions were restricted to variables for which the missing data represented only a limited fraction of the total number of patients in our cohort. Moreover, as these were retrospective data, a CT-scan looking for the diagnosis of TEE was not systematically done for all patients at D15, which may have underestimated the proportion of TEE during the stay in patients who had progressed favorably. This may have led to false negatives in CALT 2. Regarding CALT 1, however, it can be emphasized that a CT-scan result within the first 48 hours was an inclusion criterion of our study, resulting in a good reliability of the incidence of TEE at admission.

The third limitation lies in the existence of a grey zone for the CALT scores, with 35/124 subjects (28%) at D1 and 43/124 subjects (35%) at D3 for whom our protocol was unable to predict the risk of TEE. This proportion remains nevertheless limited, allowing a majority of patients to benefit from a therapy that appears to be adapted to their level of risk.

One last important limitation results from the striking changes in the epidemiology of SARS-CoV-2 infections since the appearance of the outbreak [21]. Treatments and vaccination have deeply modified the epidemiology of COVID-19 in the ICU by reducing the incidence of severe SARS-CoV2 infection. The proportion of immunocompromised patients among severe cases has strongly increased, questioning the validity of our protocol in this new setting. Further studies will be necessary to assess the performance of the protocol in the immunocompromised population.

5. Conclusions

In patients with severe SARS-CoV-2 infections, we identified specific risk factors of TEE at admission and during the ICU stay. Based on these results, we were able to establish a tool to assist the decision of curative anticoagulation during severe forms of SARS-CoV-2 infection: the CALT protocol. These results must be considered in the perspective of the changing epidemiological features of severe COVID-19, therefore requiring further studies to test the validity of our protocol.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Counts of Missing Data; Table S2: Intrinsic performance and predictive values of the CALT-1 score; Table S3: Intrinsic performance and predictive values of the CALT-2 score.

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