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ORIGINAL ARTICLE

Systematic screening for a proximal DVT in COVID-19 hospitalized patients: Results of a comparative study

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Summary
Introduction. — The COVID-19 pandemic is associated with a high incidence of venous thromboembolism questioning the utility of a systematic screening for deep venous thrombosis (DVT) in hospitalised patients.
Methods. — In this prospective bicentric controlled study, 4-point ultrasound using a pocket device was used to screen for DVT, in patients with SARS-CoV-2 infection and controls admitted for acute medical illness not related to COVID-19 hospitalised in general ward, in order to assess the utility of a routine screening and to estimate the prevalence of VTE among those patients.
Results. — Between April and May 2020, 135 patients were screened, 69 in the COVID+ group and 66 in the control one. There was no significant difference in the rate of proximal DVT between the two groups (2.2% vs. 1.5%; $P = 0.52$), despite the high rate of PE diagnosed among COVID-19 infected patients (10.1% vs. 1.5%, $P = 0.063$). No isolated DVT was detected, 37.5% of PE was associated with DVT. Mortality (7.2% vs. 1.5%) was not different ($P = 0.21$) between COVID-19 patients and controls.

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Conclusion. — The systematic screening for proximal DVT was not found to be relevant among COVID-19 patients hospitalized in general ward despite the increase of VTE among this population. Further studies are needed to confirm the hypothesis of a local pulmonary thrombosis which may lead to new therapeutic targets.

Introduction

The world is witnessing since December 2019 a global health crisis related to Coronavirus disease 2019 (COVID-19), which main clinical manifestation is severe acute respiratory syndrome. Mortality related to hospitalized COVID-19 infection is high, ranging from 5 to 20% [1—4]. In France, the estimated mortality rate is 6% mainly due to cardiac and respiratory complications of the virus. This poor prognosis has been shown to be associated with a high prevalence of venous thromboembolic events (VTE), estimated between 20 and 30% among infected patients [5,6]. In a post-mortem study, autopsies performed on COVID-19 patients found that pulmonary embolism (PE) was the direct cause of death in 33% of the cases [7]. This association can be explained by COVID-19 Associated Coagulopathy (CAC), a distinct form of coagulopathy that includes inflammation storm, endothelial dysfunction and immunothrombosis [8—10]. The prevalence of VTE in COVID-19 patients hospitalized in general ward is estimated around 10% according to recent meta-analyses [11,12], but ranges vary between 0 and 94%, with large index of heterogeneity ranges. This can be explained by the variable thromboprophylaxis strategies explained by the empiric use of intermediate or therapeutic doses for some patients [13] and most importantly by discrepancies in the screening strategy for VTE between centres.

Some study groups have advocated a systematic screening for Deep Venous Thrombosis (DVT) [6,14,15] for ICU-patients suffering from Acute Respiratory Distress Syndrome (ARDS). However, little is known about the utility of such strategies in general ward patients. Nopp et al. reported that systematic ultrasound screening in general ward showed a remarkably high rate of DVT 23% ([95%CI: 3.2—52.5]) [12]. This finding questions about the screening in this population. Therefore, given a significant increased mortality in patient with VTE [16,17], we can assume that early detection of DVT complication could reduce the embolic risk and therefore the mortality associated with the COVID-19. However, because no study had a control group, the real – risk of DVT in this population and the benefit of its screening remains unknown.

Thus, we conducted a prospective open-label controlled study, in which all new COVID-19 patients (COVID+) admitted in general ward of two hospital centres in the region of Normandy in the west of France were screened for DVT and compared to a group of non-COVID-19 (COVID-) patients with similar baseline, clinical and biological characteristics. The main purpose of this study was to assess the utility of a routine screening for proximal DVT among COVID-19 patients hospitalised in general ward. Moreover, we aimed to estimate the prevalence of VTE among those patients compared to COVID- and identify clinical or biological risk factors of developing DVT, in order to adjust the screening strategy among infected patients.

Material and methods

Study design

This was a prospective open-label controlled bicentric trial. The study was approved by the Institutional Ethical Committee (20.04.03.44507) and patients or their legal representative gave standard oral consent.

Patients

Consecutive adult patients with COVID-19 who have been admitted to the University Hospital Centre of Rouen and the Hospital Centre of Dieppe, in general ward, between the 6th of April and the 10th of May were enrolled in the COVID+ group. In parallel, patients admitted for an acute medical inflammatory affection unrelated to COVID-19 disease in general ward (in internal medicine and infectious diseases departments) at the same period were enrolled in the control group.

COVID-19 infection was diagnosed with either a positive real-time-transcriptase polymerase chain reaction (RT-PCR) for COVID-19 using nasopharyngeal swab or a high likelihood of COVID-19 on thin-section computed tomographic CT of the chest [18]. Patients were excluded if they were on therapeutic dose of anticoagulant.

Outcome

The primary outcome was the incidence of symptomatic and asymptomatic proximal DVT found on pocket-sized ultrasound device. DVT was defined by the lack of a vein compression in a systematic 4-point compression ultrasonography (CUS) with pocket-sized ultrasound devices (CUS-PUD) screening.

The secondary outcome was the incidence of either PE or DVT (regardless symptoms).

Outcome assessment

All patients underwent systematic bilateral 4-point CUS-PUD (V-Scan Dualprobe©, GE Healthcare, Milwaukee, Wisconsin, USA) for proximal lower limb DVT at day 0(+1), 7(±1) from the hospital admission and at discharge. CUS-PUD was performed according the previously described protocols [19] by 4 trained physicians (YF, CES, AB, JL). If PE was suspected diagnosis was based on CTPA.

We collected for all patients their clinical risk factors for VTE which implies their age, personal or familial VTE background, and BMI. We also checked at each visit their laboratory findings (platelet count, D-dimer, prothrombin time, fibrinogen level and C-reactive protein), and the occurrence of a poor outcome, defined by death or the need of a transfer to an ICU unit.

Statistical analysis

DOQBOARD software (Mont Saint Aignan, FRANCE) was used to collect data. SPSS Statistics Software (SPSS Inc., Chicago, IL, U.S.A.) were used to conduct the statistical analyses. Continuous variables are presents as the means and standard deviations, and categorical variables are presented as numbers and percentages. The differences between groups in relation to the continuous variables were analysed using the Student's t-test for parametric values and a Mann-Whitney U test for non-parametric ones. Pearson's chi-squared test and Kruskall Wallis's test were used to analyse the difference between groups in relation to the categorical variables respectively for the parametric and non-parametric values.

Results

Demographic and clinical description

Between April and May 2020, 69 patients with COVID19 disease were recruited and matched with 66 controls. In the control group, 3 patients were excluded from analysis because they were admitted for scheduled hospitalization, 69% of the remaining patients had an infectious disease of which 68% were respiratory. In the infected group, the mean age was 63 years old (±17.6), a BMI at 28 ± 5.7 and 39.4% were men, with no difference compared to the COVID- patients. Medical history and VTE risk factors were similar in both groups. Baseline characteristics of the study population are summarized in Table 1.

Compared to controls, COVID+ patients had similar levels of the main parameters of coagulation at admission with an increase in D-dimer level [2175.92(IQR 1583.5) versus 1294.32 (IQR 842); $P = 0.10$], an inflammatory state and a normal rate of platelet count and of prothrombin time in both groups (Table 1).

Most patients received thromboprophylaxis but a significantly higher rate of patients in the control group were not on thromboprophylaxis compared to COVID group (19.7% versus 2.9%; $P = 0.002$). Standard dose (Enoxaparin 40 mg daily or subcutaneous heparin 5000 UI per 12 h were administered to 93 (68.9%) patients, while 22 (16.3%) received intermediate dose (enoxaparin 60 mg, 40 mg per 12 h or subcutaneous heparin 5000 UI per 8 h). Intermediate dose regimen was significantly more frequent in the COVID group (23.2%) than in the control (9.1%) $P = 0.035$.

Outcome

Among the 135 patients enrolled 3 (2.2%) were diagnosed having a DVT on CUS-PUD. In the COVID+ group, 2 patients experienced DVT (2.9%) and 1 (1.5%) patient had a DVT in the control group ($P = 0.52$). All the positive CUS-PUD were found at the first assessment between day 0 and day 1. No DVT was diagnosed during follow up at day 7 or at discharge. Only one out of the three patients with DVT were symptomatic. PE was diagnosed in 8 patients, 7 (10.1%) in the COVID+ group and 1 (1.5%) in the control group ($P = 0.63$). In all cases but 1 the diagnosis of PE was performed the day of admission. The mean time between the onset of COVID symptoms and the PE was 13.28 (±8.08) days.

All cases of acute lower limb DVT on CUS-PUD were associated with a PE. On the other hand, despite the similar screening strategy in both groups, a higher rate of isolated PE was found among COVID-19 patients (71.42%) compared to the control ones (0%). In fact, there was no significant difference between the numbers of computed tomography pulmonary angiogram (CTPA) performed between both groups (46.37% vs. 40.90%, $P = 0.60$). In the COVID+ group, 25% of the patients who underwent CTPA were diagnosed with PE.

Death occurred in 7.2% of COVID+ patients but there was no significant increase in the mortality rate compared to 1.51% in the COVID- group ($P = 0.209$) (Table 2). The mortality was not statically different according to the diagnosis of PE (8.1%) or not (0%) in the COVID+ group.

Discussion

In this bicentric controlled study there was no significant difference in the incidence of proximal DVT between COVID-19 patients and those from a control group recruited in general ward. With a 10.14% rate of PE in patients with COVID-19 compared to 1.5% in the control group, our study comforts the hypothesis of a particular thrombotic risk associated with COVID-19 infection despite a more extensive thromboprophylaxis coverage at intermediate and/or standard dose. Most patients were free from proximal DVT at the diagnosis of PE, and no isolated DVT was diagnosed in our cohort. Moreover, there were no proximal DVT diagnosed in the follow up suggesting that a whole leg screening on admission would not have been clinically relevant.

We focused our study on patients admitted in general ward because the data of thrombotic complications in this specific population are lacking compared to patients in intensive care unit. Recent papers have suggested a strategy against systemic DVT screening in non-ICU patients despite the absence of prospective controlled data [10,20]. A pocket-sized device was selected as a screening tool because of its portable technology, which makes it easier to use and allow physicians to perform the exam at bedside, avoiding patients transport. 4 points CUS- PUD has already proven its good sensitivity and specificity for the diagnosis of DVT, compared to whole leg ultrasound [21].

In order to describe the specific risk associated to COVID 19 infection we performed a similar real-time screening strategy in a control group of patients admitted in Internal Medicine or Infectious Disease units, with an acute medical illness. This group of patients had a similar inflammatory state to those who were infected with COVID-19 and thus a

Table 1 Baseline characteristics of the study population.

	All patients ($n = 135$)	COVID+ ($n = 69$)	COVID− ($n = 66$)	*P*	OR (95%IC)
Demographic characteristics					
Age	63.6 ± 17.5	63.3 ± 17.6	63.0 ± 17.6	0.87	
Male sex (%)	58 (43%)	27 (39.1%)	31 (47.0%)	0.39	1.37 (0.69—2.73)
BMI	27.3 ± 6.0	28.0 ± 5.7	26.6 ± 6.3	0.22	
VTE Risks factors					
BMI > 30	36 (27.3%)	23 (34.3%)	13 (20%)	0.08	2.09 (0.94—4.61)
BMI > 40	3 (2.3%)	1 (1.5%)	2 (3.1%)	0.62	0.47 (0.04—5.39)
Personal history of VTE	13 (9.6%)	7 (10.1%)	6 (9.1%)	1	1.13 (0.36—3.55)
Familial history of VTE	7 (5.2%)	3 (4.3%)	4 (6.1%)	0.71	0.71 (0.15—3.28)
Active Cancer	12 (8.9%)	6 (8.7%)	6 (9.1%)	1	0.95 (0.29—3.1)
Hormonal treatment	5 (3.7%)	3 (4.3%)	2 (3.0%)	1	1.45 (0.24—8.99)
Anticoagulant treatment					
Prophylactic dose[a]	93 (68.9%)	47 (68.1%)	46 (69.7%)	0.86	0.93 (0.93—1.93)
Intermediate dose[b]	22 (16.3%)	16 (23.2%)	6 (9.1%)	**0.035**	**3.02 (1.1—8.3)**
No anticoagulation	14 (10.4%)	1(1.4%)	13 (19.7%)	**< 0.001**	**0.06 (0.08—0.47)**
Laboratory test					
Platelet count ($\times 10^9$/L)	236.4 ± 104.1	224 ± 96.2	248.9 ± 111.1	0.17	
Prothrombin time (PT) (%)	89.9± 15.1	91.3 ± 15.9	88.3 ± 14.2	0.28	
CRP (mg/L)	85.8 ± 97.9	86.2 ± 93.7	85.3 ± 102.7	0.96	
Fibrinogen (g/L)	8.0 ± 13.7	5.0 ± 1.9	10.3 ± 18.1	0.42	
D-dimer (ng/mL)	1847 ± 2128.8	2175.9 ± 2510	1294.3 ± 1091.8	0.10	

P < 0.05 were considered significant and were in bold.
[a] Enoxaparin 40 mg.
[b] Enoxaparin 40 mg × 2, Enoxaparin 60 mg, Enoxaparin 60 mg × 2, Calciparine 5000 UI × 3.

Table 2 Clinical outcomes.

	All ($n = 135$)	COVID+ ($n = 69$)	COVID− ($n = 66$)	*P*	OR
DVT V-scan	3 (2.2%)	2 (2.9%)	1 (1.5%)	0.52	1.94 (0.17—21.92)
VTE (PE and/or DVT)	8 (5.92%)	7 (10.1%)	1 (1.5%)	0.063	7.34 (0.88—61.38)
Isolated PE	5 (62.5%)	5 (71.4%)	0 (0%)	0.38	6.6 (0.19—226)
Isolated DVT	0	0	—	—	—
Symptomatic DVT	0 (0.00%)	0 (0.00%)	0 (0.00%)	—	—
Symptomatic PE	7 (5.2%)	6(8.7%)	1(1.5%)	0.12	6.19 (0.73—52.88)
Death	6(4.4%)	5(7.2%)	1(1.5%)	0.209	5.08 (0.58—44.68)

similar procoagulant state regarding thrombosis risk factors other than COVID-19 disease.

Our strategy of performing a proximal 4-point CUS repeated CUS at 1 week has already shown its relevance with a similar 3-month rate of VTE as the complete single CUS (0.9% vs. 1.2%) and a comparable safety, while being less costly and time consuming [22], which already lead to question the relevance of treating calf DVT with therapeutic anticoagulation. Moreover, we found no new DVT in the repeated exams at day 7 and before discharge confirming the absence of extension of a distal DVT to the proximal veins.

Our study is representative of COVID-19 patients requiring general ward hospitalization. Except for the higher rate of women that was not found in other studies, the patient included in our cohort had similar clinical and biological characteristics than other published cohorts Table 3. Moreover, the mortality rate (7.2%) is consistent with the national rate at that time.

In our study, incidence rate of DVT in the COVID+ patients were 2.9% which is lower than previously reported in prospective cohorts. This apparent discrepancy is probably explained by the fact that we focused DVT screening on the proximal area while other study found up to 30% of below knee DVT. To detect hypothetic extension of undiagnosed distal DVT in our cohort we have prospectively followed the patients at day 7 and at discharge. We failed to demonstrate new DVT on this ultrasound confirming the absence of extension of an hypothetic distal DVT to the proximal veins. Similar results were found in prospective cohorts conducted in general ward of confirmed COVID-19 patients. Authors showed a rate of proximal DVT between 0.6 to 4.5% among a rate of DVT between 11.9 to 14.7%. Given the absence of new proximal event during our follow up our

Table 3 Comparison between our population characteristics and outcomes and other general ward cohorts.

Author	Type of study	Control group	Sample size	Mean age	Sex (% male)	% of patient who underwent CUS	Thrombo-prophylaxis	Mortality	VTE (PE or DVT)	PE in Covid+	DVT (lower limbs)
Our study	Prospective	Yes	69	63.33 ± 17.6	39.13%	100% CUS-PUD repeated at day 7 and at discharge	97.10%	7.24%	10.14%	10.14%	Proximal 2.89%
Santoliquido et al. [31]	Prospective	No	84	67.6 ± 13.5	72.6%	100% CUS	100%	9.5%	/	/	Overall: 11.9% (4.98—18.82) Proximal: 2.4% Distal: 9.5%
Demelo-Rodríguez et al. [32]	Prospective	No	156	68.1 ± 14.5	65%	100% CUS	98.1%	/	/	/	Overall 14.7% Proximal: 0.6% Distal 4.5%
Avruscio et al. [33]	Prospective	No	44	67 ± 14	64%	100% CUS repeated weekly	100%	4.5%	27.3% (including upper limb and int jugular)	0%	Overall 13.63% Proximal 4.54% Distal
Middledrop et al. [25]	Retrospective	No	123	60 ± 16	59%	If symptomatic 8.65% CUS	100%	/	3.3% symptomatic	1.6%	Proximal 0% Distal 1.6%
Stephan et al. [5]	Retrospective	No	539	/	/	/	81%	20%	1.9%	1.52%	0.4% isolated DVT or SVT
Cattaneo et al. [30]	Retrospective	No	64	70(IQR: 58—77.5)	54.68%	100% CUS	100%	/	/	/	0
Zhang et al. [34]	Retrospective	No	143	63 ± 14	51%	89.93% CUS	37.1%	22.4%	/	/	Overall 46.15% Proximal: 16.08% Distal: 30.06%
Lejeune et al. [35]	Retrospective	No	42	65 ± 19	55%	100%	59.5%	4.8%	26%	9.5%	Proximal 2.38% Distal 16.66%
Mazzaccaro et al. [36]	Retrospective	No	32	68.6	71.9%	100% CUS	100%	9.4%		65.6%	Proximal 3.12%
Reichert et al. [37]	Prospective	No	83	67.6 [56.4—80.2]	64.5%	100% CUS	99.07%	Unknown	Unknown	Unknown	14.5%

results suggesting that asymptomatic distal DVT in hospitalized is not clinically relevant in COVID-19 patients. In our study, comparatively to previously published cohort studies performed in the same population, we have found a higher prevalence of PE in COVID-19 patients (10.1%) (Table 3). This difference is probably related to the fact that we have systematically excluded patients treated with therapeutic dose of anticoagulation at admission. The other reason is that while the study was performed the medical world was particularly concerned about the VTE risk. In fact, almost half of our patients underwent a CTPA to screen for PE at admission particularly if they required oxygen therapy. In previous study, PE screening test was less exhaustive with only 8.7% and 11.3% of CTPA performed respectively in the studies of Middledorp et al. and Lodigiani et al. [23,24].

Systematic DVT screening

The results of a recent systematic review support the screening given increased rate of DVT diagnosed from 1.4% (95%CI:0.7—2.3) to 12.7% (95%CI:3.7—25.5%) when ultrasound screening was performed [12]. However, studies included in this review were heterogeneous, most of them were retrospective studies with patients recruited in an intensive care unit and in general ward indistinctly [25—27]. Importantly prophylaxis coverage was sometimes very low and most of the patients should have received a prophylaxis [28]. Finally, high DVT rate seem to be largely accounted by asymptomatic distal DVT, as the prevalence of proximal DVT ranged between 0 to 3% which is consistent with our findings. In our prospective controlled study, we found a similar rate of proximal rate of DVT than in the control group suggesting that in this population systemic DVT screening is useless.

Another important finding of our study is that PE is overrepresented compared to DVT and isolated PE represents almost two-thirds of PE while no DVT diagnosed were isolated. Similar finding has previously been described [6,29,30] and raise the question of a localized thrombotic microangiopathy that would be responsible of in situ pulmonary thrombosis rather than venous thromboembolism as it usually occurs in VTE. In fact, it is unknown whether thromboprophylaxis can prevent this kind of thrombotic disorder. Moreover, guidelines and several teams suggest increasing the dose of anticoagulant while the benefit risk ratio is largely unknown.

Limitations and strength

Our study has some limitations and strength. First our sample size is relatively small. Secondly, we did not confirm the results of our pocket size 4-point ultrasound with a whole leg ultrasound.

One of the strength of our study is the prospective and bicentric design. Moreover, to our knowledge, our study in the only one comparing in real-time a group of COVID-19 patients to a similar population of patients hospitalized for an acute inflammatory medical affection with a follow up of both groups until discharge. Both groups had a similar screening strategy for DVT and for PE and thromboprophylaxis recommendations were applied in both groups. This allows us to overcome the heterogeneity issue that make us questions the reliability of the conclusions in previous studies.

Conclusion

In conclusion, our study confirms the absence of relevance for a systematic DVT screening in COVID-19 patients hospitalized in general ward. In fact, our results confirmed the low prevalence of proximal DVT with no significant increase in proximal DVT among COVID-19 infected patients compared to patients hospitalized in general ward for another acute medical.

Our results therefore comfort the hypothesis of a local pulmonary thrombosis rather than the classical venous thromboembolism. Whether this hypothesis should lead to change the current ''high dose'' anticoagulation strategy remains to be clarified by further studies.

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Author contribution

YF, YCSE, AB and JL and SM performed the research. YF and SM performed the research, analyzed data, performed data analysis and wrote the manuscript. PB, GA, KA, MG, HL and YB, interpreted the data, and provided critical review of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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