Coronavirus disease 2019 is associated with catheter-related thrombosis in critically ill patients: a multicenter case-control study

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1. Introduction

Since its emergence in December 2019, the coronavirus disease 2019 (COVID-19) epidemic rapidly progressed into a pandemic. A noticeable observation in critically ill patients affected by COVID-19 pneumonia is the high incidence of thrombotic complications, especially that of pulmonary embolism [1]. A possible explanation for the hypercoagulable state is an overproduction of early response proinflammatory cytokines, causing activation of coagulation pathways [2]. Available evidence suggests that the coagulopathy associated with COVID-19 is a combination of low grade disseminated intravascular coagulation and localised thrombotic microangiopathy [3,4]. These findings prompted multiple ICUs in the Netherlands to increase thromboprophylaxis dosage. However, the exact pathophysiology of COVID-19 associated hypercoagulability remains unclear and as increased thrombosis prophylaxis may not prevent pulmonary immunothrombosis, better knowledge of COVID-19 associated hypercoagulability is warranted [5].

Importantly, the majority of patients admitted to the intensive care unit (ICU) receive a central venous catheter (CVC) of which a considerable proportion develops catheter-related thrombosis (CRT). This is considered a serious complication as it may cause pulmonary embolism, increases the risk of infections, can cause catheter dysfunction or long-term central venous stenosis, and is associated with considerable healthcare costs [6,7]. When considering COVID-19 coagulopathy to cause an overall hypercoagulable state rather than mainly a local prothrombotic state in the pulmonary circulation, COVID-19 is presumably also associated with CRT in critically ill patients with an indwelling CVC. In this multicenter case-control study we set out to investigate the association of COVID-19 with CRT, under the hypothesis that COVID-19 predisposes to CRT in critically ill patients.

2. Materials and methods

2.1. Design

This was a multicenter case-control study conducted at the ICUs of Amsterdam UMC, location VUmc and AMC, Leiden UMC, and Tergooi hospital, Hilversum, in The Netherlands; three tertiary centers and one secondary center. All ultrasound data was collected during routine care by the treating physicians and in compliance with COVID-19 hospital regulations. The study was approved and the necessity for informed consent was waived by the institutional review boards. An opt-out procedure was used. STROBE-guidelines were followed [8].

2.2. Population and procedures

The study population consisted of adult (≥18 years) patients admitted to the ICU of the participating hospitals between April 13, 2020 and May 13, 2020. Patients were included if they had an indwelling or recently removed (≤48 h) CVC of the internal jugular, subclavian or femoral vein. To obtain CRT prevalence, all patients admitted at a specific time-point were cross-sectionally enrolled by the treating physicians within a time frame of 1–5 days per site. To minimize the confounding effect of catheter-indwelling time, patients were excluded if catheter indwelling-time was less than 48 h.

Notably, during the conduct of the study, standard dosage thromboprophylaxis was doubled for COVID-19 patients – i.e. 2800 IU nadroparin twice daily or 5700 IU nadroparin once daily for patients with a body weight under 100 kg – leading to a situation in which some included COVID-19 patients received standard and some double dosage thromboprophylaxis at time of CVC insertion.

Multiple certified operators performed one compression and duplex ultrasound examination of the CVC entry vein per included patient. CVC entry veins were scanned by compressing every 2 cm and duplex ultrasound was used to assess residual flow. The vein failing to collapse at any point, an echogenic thrombus or an intraluminal filling defect was considered diagnostic for CRT. The internal jugular vein was visualized in both axes along its length from the mandible downward to the supraclavicular fossa at the junction with the subclavian vein. The subclavian vein was visualized in both axes from the manubrium until the transition into the axillary vein. The femoral vein was visualized in both axes from 5 cm below the insertion site upwards to inguinal ligament. Cases were defined as patients with a confirmed diagnosis of CRT. The control group consisted of patients with CRT ruled out.

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Table 1
Baseline characteristics and primary outcome.

Variables	Overall n (%), mean (±SD), median [IQR]	CRT − n (%), mean (±SD), median [IQR]	CRT + n (%), mean (±SD), median [IQR]
Baseline characteristics			
Sex			
• Male	66 (80.5)	52 (81.2)	14 (77.8)
• Female	16 (19.5)	12 (18.8)	4 (22.2)
Age, years	63.0 [54.5, 70.0]	62.5 [53.0, 70.0]	63.0 [59.5, 70.5]
BMI, kg/m^2	27.9 (±4.4)	27.8 (±4.7)	28.4 (±2.8)
SOFA-score	8.7 (±3.5)	8.6 (±3.4)	9.1 (±3.8)
Duration of ICU admission, days	23.3 (±8.4)	24.7 (±8.6)	19.6 (±6.5)
Duration of ventilation, days[a]	13.0 [10.0, 20.0]	14.0 [11.5, 21.0]	10.0 [9.0, 13.0]
Insertion site			
• Internal jugular vein	65 (79.3)	49 (76.6)	16 (88.9)
• Subclavian vein	1 (1.2)	1 (1.6)	0 (0.0)
• Femoral vein	16 (19.5)	14 (21.9)	2 (11.1)
Blood test results			
• CRP, mg/L	168.0 [110.1, 247.8]	152.0 [87.8, 230.7]	243.0 [175.8, 325.0]
• Haemoglobin, mmol/L	6.9 (±1.4)	6.6 (±1.3)	7.7 (±1.4)
• Platelets, $\times 10^9$/L	312.7 (±149.8)	312.7 (±151.4)	312.6 (±148.8)
• WBC, $\times 10^9$/L	11.6 [7.9, 15.6]	11.6 [7.8, 17.2]	10.8 [8.0, 13.6]
• PT, s	11.9 [11.1, 15.1]	12.0 [11.2, 15.9]	11.4 [11.0, 12.2]
• APTT, s	28.0 [24.0, 39.4]	33.0 [24.0, 44.7]	25.0 [24.0, 28.0]
Primary outcome			
COVID-19			
• No	20 (24.4)	19 (29.7)	1 (5.6)
• Yes	62 (75.6)	45 (70.3)	17 (94.4)
Anticoagulant dosage during CVC insertion			
• Standard prophylactic dosage	32 (39.0)	16 (25.0)	16 (88.9)
• Double prophylactic dosage[a]	19 (23.2)	18 (28.1)	1 (5.6)
• Therapeutic dosage	29 (35.4)	28 (43.8)	1 (5.6)
• None	2 (2.4)	2 (3.1)	0 (0.0)
Catheter indwelling-time, days	12.0 [7.0, 17.8]	13.0 [7.0, 20.0]	10.0 [8.2, 11.8]

Table depicts baseline characteristics and primary outcome. Time variables, e.g. duration of ICU admission, indicate time until ultrasound examination, whereas anticoagulant dosage and blood test results resemble results at time of CVC insertion. '−' denotes absence of disease and '+' denotes presence of disease.
APTT: activated partial thromboplastin time; BMI: body mass index; CI: confidence interval; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CRT: catheter-related thrombosis; CVC: central venous catheter; ICU: intensive care unit; INR: international normalized ratio; PT: prothrombin time; SD: standard deviation; SOFA: sequential organ failure assessment; WBC: white blood cell count.
[a] Data only applicable to or available from COVID-19 patients.

2.3. Outcomes

The primary outcome was CRT as diagnosed by vascular ultrasound. The exposure of interest was COVID-19 pneumonia as defined by a positive result of a reverse transcription polymerase chain reaction assay (RT-PCR) for SARS-CoV-2 and corresponding clinical features or abnormalities on thoracic imaging. For ICU patients to be deemed COVID-19 negative, a negative RT-PCR of an oropharyngeal swab sufficed for patients without any clinical features of COVID-19 and a negative RT-PCR of a bronchoalveolar lavage sufficed for suspected COVID-19 patients. Due to the high incidence of thrombotic complications in COVID-19 patients and the increased thromboprophylaxis intensity, anticoagulant usage was predefined as potential confounder. Moreover, as cumulative incidence of CRT increases until CVC removal, another predefined confounder was catheter indwelling-time.

2.4. Statistical analysis

A sample size of 56 was calculated by using a power of 0.80 and an α-risk of 0.05. Expected prevalence of CRT (cases) was 30% [9]. We expected 80% of all cases and 40% of the controls to be admitted because of COVID-19 pneumonia [1]. To account for data loss and confounders we aimed to include around 80 patients.

To assess distribution, histograms and Q-Q plots were evaluated. Normally distributed data are expressed as mean ± standard deviation (±SD). Non-parametric data are expressed as median and interquartile range [IQR]. The association of COVID-19 with CRT was tested in a univariate and multivariate logistic regression model, adjusted for the predefined confounders. Odds ratios (ORs) are reported with 95% confidence intervals (CIs). All analyses were performed in R via RStudio (RStudio Team, Inc., USA).

3. Results and discussion

Ultrasound examinations were performed consecutively in 87 critically ill patients. In three patients catheter-indwelling time was unknown due to hospital transfer with already an indwelling CVC and an unknown insertion date. Catheter indwelling-time was less than two days in two patients, leaving 82 patients for the final analysis (Supplemental file 1). The majority of patients was male (80.5%) and with a median age of 63.0 [IQR: 54.5, 70.0] years. Baseline characteristics and differences among controls and cases are depicted in Table 1 and Fig. 1a. The majority of patients (76%) was diagnosed with COVID-19.

The overall prevalence of CRT was 22%. Of the 18 patients with CRT, 17 were admitted because of COVID-19 pneumonia, 16 received standard dosage thromboprophylaxis, one received double dosage thromboprophylaxis, and one received therapeutic anticoagulant therapy. Median catheter indwelling-time in patients with CRT was 10 days [IQR: 8.2, 11.8]. In cases versus controls, the crude OR for CRT, given COVID-19 exposure, was 7.2 (95% CI: 1.32, 130). The OR for CRT, given COVID-19 exposure adjusted for anticoagulant usage and catheter indwelling-time, was 18.3 (95% CI: 2.31, 410).

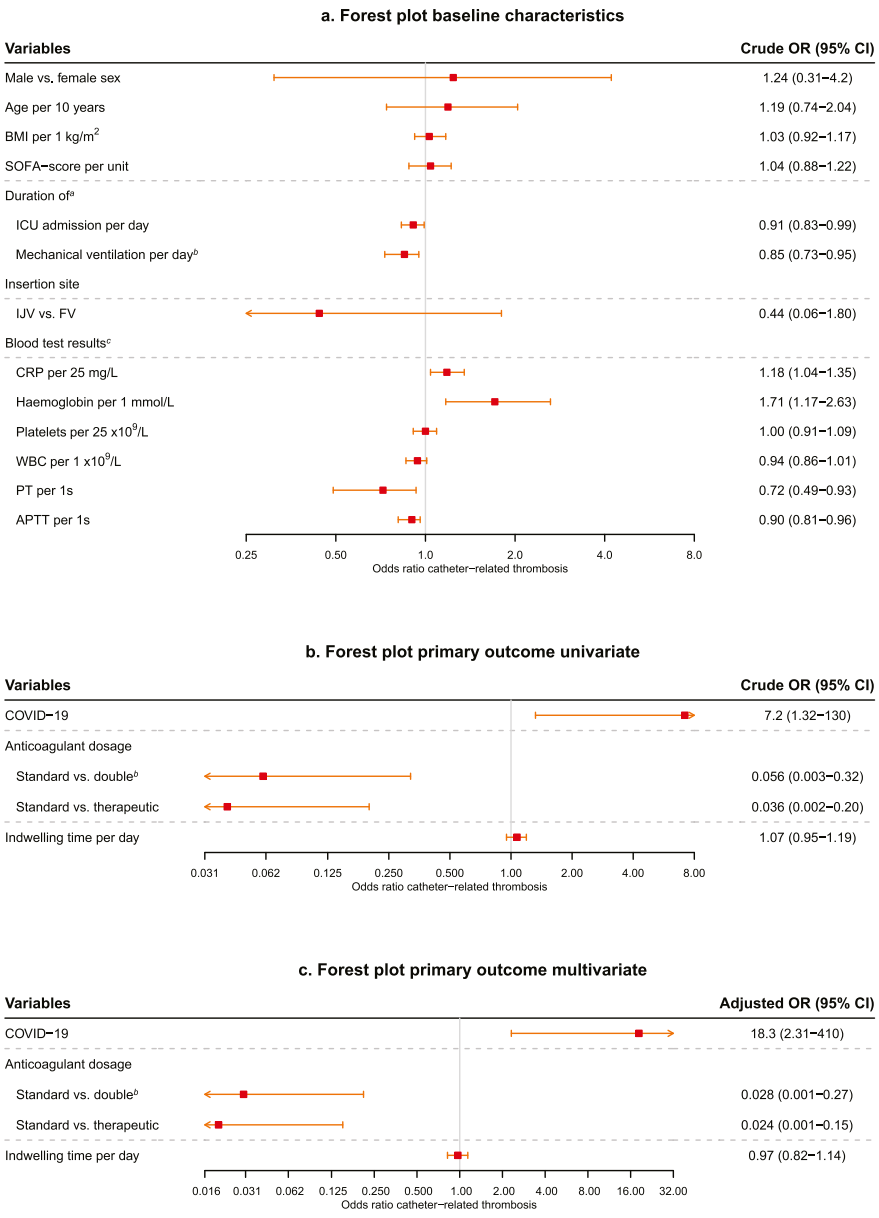

Fig. 1. Forest plots of baseline characteristics (1a), univariate and multivariate analysis of primary outcome (1b and 1c). Crude and adjusted odds ratios are shown with their respective 95% confidence interval. Continuous variables are shown as per 'one' increase unless specified otherwise. Model likelihood-ratio test: $X^2 = 34.65$, df = 5, $p < 0.0001$; Nagelkerke $R^2 = 0.53$.
[a]: time until ultrasound examination.
[b]: data only applicable to or available from COVID-19 patients.
[c]: at time of CVC insertion.
APTT: activated partial thromboplastin time; BMI: body mass index; CI: confidence interval; COVID-19: coronavirus disease 2019; CRP: C-reactive protein; CRT: catheter-related thrombosis; CVC: central venous catheter; Double: double prophylactic; FV: femoral vein; ICU: intensive care unit; IJV: internal jugular vein; INR: international normalized ratio; OR: odds ratio; PT: prothrombin time; Ref: reference; SD: standard deviation; SOFA: sequential organ failure assessment; Standard: standard prophylactic; WBC: white blood cell count.

The crude ORs for CRT, given standard versus double dosage thromboprophylaxis and standard thromboprophylaxis versus therapeutic anticoagulation, were 0.056 (95% CI: 0.003, 0.32) and 0.036 (95% CI: 0.002, 0.20), respectively. Catheter indwelling-time was not associated with CRT, for a crude OR of 1.07 (95%CI: 0.95, 1.19) per day increase (Fig. 1b). In the multivariate analysis, the adjusted OR for CRT, given standard versus double dosage thromboprophylaxis and standard thrombosis prophylaxis versus therapeutic anticoagulation, was 0.028 (95% CI: 0.001, 0.27) and 0.024 (95% CI: 0.001, 0.15), respectively. Moreover, the prevalence of therapeutic anticoagulation in patients with COVID-19 (35%; 22/62) was the same as in patients without COVID-19 (35%; 7/20), underlining the strong association of COVID-19 with CRT. Adjusted OR for CRT, given catheter indwelling-time, was 0.97 (95% CI: 0.82, 1.14) (Fig. 1c).

The main finding of this multicenter case-control study is that COVID-19 indeed predisposes to CRT in critically ill patients. These results are in line with previous research investigating thrombotic complications in critically ill patients [1]. The strong association of COVID-19 with CRT seems to confirm the suggestion of an overall hypercoagulable state, but, due to study design, causation cannot be inferred. It also underlines the fact that explanatory bonds between the COVID-19 induced-immune response and hypercoagulability are yet to be completely elucidated. A recent autopsy study showed extensive immunothrombosis over a wide pulmonary (micro)vascular territory, suggesting local pulmonary vascular endotheliopathy as a potential cause for the high incidence of pulmonary embolism, whereas the association of COVID-19 with CRT and other deep venous thrombosis suggests a more diffuse pro-thrombotic state, thought to be caused by a profound inflammatory state during acute lung injury [4,10].

Interestingly, in line with the suggestion of a diffuse pro-thrombotic state, higher than standard prophylactic doses of anticoagulation at time of CVC insertion – i.e. at time of endothelial injury and reduction of blood flow in the entry vein – seemed to attenuate the association of COVID-19 with CRT (Supplemental file 2). Of note, due to study design, these results should be interpreted with caution as any beneficial effects on outcome of double dosage thromboprophylaxis cannot be extrapolated. The efficacy and safety of heightened intensity thromboprophylaxis should be investigated in a randomized controlled manner (e.g. NCT04380779, NCT04360824, NCT04345848 and NCT04367831).

The strength of our study is its multicenter and case-control design.

However, because of its design, relevance of CRT for prognosis of outcome could not be assessed. Moreover, we reported large confidence intervals as CRT occurrence was low in an absolute sense. One or two additional cases of CRT could have influenced the ORs. Even so, as we found higher odds for CRT in COVID-19 patients, despite higher intensity anticoagulation, we think this not significantly affects the validity of our conclusion.

In conclusion, COVID-19 showed to be highly associated with CRT in critically ill patients.

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Availability of data and materials

Data is available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Approval was given by the local ethics committee (METc VUmc). Necessity for informed consent was waived and an opt-out procedure was used for data collection.

Guarantor statement

Jasper M. Smit takes responsibility for the content of the manuscript, including the data and analysis.

CRediT authorship contribution statement

JS, FK, MH and PT were responsible for the conception and design of the study. JS, JM, RV, MM, KFC, FB, AV, CK, DW and PT were responsible for acquisition of the data and construction of the database. JS, FK, MH and PT were responsible for the data analysis. JS and PT were responsible for drafting the manuscript and all authors provided critical revisions for it. All authors read and approved the final manuscript and ensured that questions regarding the accuracy or integrity of any part of the work were investigated and resolved.

Declaration of competing interest

All authors declare to have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.01.013.

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