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Letter to the Editors-in-Chief

Bacterial surinfection and venous thromboembolism in critically ill ICU patients with COVID-19: What is the relationship?

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2020 will forever be remembered as the year marked by the worst global health crisis in a century due to the current Coronavirus disease 2019 (COVID-19/SARS-CoV-2) pandemic. The vast majority of patients with severe COVID-19 initially presents with single organ failure, i.e. hypoxemic respiratory failure [1]. A growing body of research suggests that severe COVID-19 infection, despite routinely low dose pharmacological venous thromboembolism (VTE) prophylaxis with Low Molecular Weight Heparins (LMWH), is associated with a high incidence of thromboembolic phenomena [2,3]. Acute bacterial infection is another well-described cause of venous thromboembolism [4,5]. Bacterial co-infection is relatively infrequent in hospitalized patients with COVID-19 but more common in critically ill patients (8.1%) [6]. We wondered if there is, independently from the causal relationship between SARS-CoV-2 and elevated thrombosis risk, also a superimposed clear association between bacterial co-infection in COVID-19 patients admitted to the ICU and thrombosis risk. In view of the fact that many of those patients suffer from multiple episodes of co-infections, it would be additionally interesting to assess whether an association between total number of co-infection episodes and thrombosis risk could be found. Therefore, we investigated if there is a relationship between the number of diagnosed VTEs and the number of episodes of bacterial co-infections in COVID-19 patients admitted to the ICU.

1. Methods

In this monocentric, investigator-initiated, longitudinal, retrospective, observational cohort study, all patients diagnosed with COVID-19 pneumonia and admitted to the ICU department of the Jessa Hospital, Hasselt, Belgium from 13th March 2020 until 17th October 2020 were enrolled. This study was approved by the ethical committee of Jessa Hospital on 14th April 2021 (2021037) and registered on clinicaltrials.gov (NCT04877808). In light of the urgent need to collect data in the ongoing pandemic, written informed consent was waived. Only laboratory-confirmed patients were included in the analysis. Laboratory confirmation of COVID-19 infection was defined as a positive result on polymerase chain reaction (PCR) assays of nasopharyngeal swab samples or on bronchoalveolar lavage. Data from consecutive COVID-19 patients admitted to ICU were prospectively entered into a customized database including medical history, demographic data, clinical symptoms and signs, laboratory results and outcomes. Data on etiology and number of co-infection episodes were recorded. Co-infections were categorized into pneumonia (including ventilator-assisted pneumonia (VAP)), bacteremia and catheter-related bloodstream infection. Bacteremia was defined as the presence of bacteria in the bloodstream that are alive and capable of reproducing and catheter-related blood stream infection as isolation of the same microorganism with identical antibiogram in the bloodstream as the one recovered from the catheter tip. This dataset was retrospectively reviewed.

All COVID-19 patients were treated according to the COVID-protocol of the JESSA, based on the latest insights on COVID-19 [7]. All patients admitted to ICU from March 13th 2020 until March 30th 2020 received routine low dose pharmacological VTE prophylaxis, i.e. once-daily subcutaneous injection of nadroparin calcium 2850 IU. Based on our own observation [3], an individualised, more aggressive thromboprophylaxis protocol was implemented on March 31st including close to therapeutic LMWH dosing and individually tailored with routine anti-Xa measurements [8]. Furthermore, all patients were systematically screened two times a week for the presence of DVT in the large veins (i.e. the inferior caval vein, iliac, femoral, popliteal, jugular, subclavian and brachial veins) with duplex ultrasonography, regardless of clinical suspicion. This technique uses a combination of a venous compression ultrasound and a venous Doppler ultrasound and was consequently performed bedside by a radiologist. Total number of thrombi locations was recorded in the database. Data set was closed at November 10th 2020.

Continuous data are shown as mean ± standard deviation (SD) and categorical data are presented as frequencies and percentages (%). The data were analyzed by means of logistic regression analysis. To compare the risk of developing bacteremia, pneumonia (including VAP) or catheter-related bloodstream infection for patients with and without VTE logistic regression models were used. Age, gender, BMI, and therapy with mechanical ventilation were incorporated as explanatory (confounding) variables in the multiple logistic models. These adjustment variables were chosen since they are potentially associated with VTE. A p-value < 0.05 is considered statistically significant. All analyses were conducted with SAS software, version 9.4 of the SAS System for

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Table 1
Baseline characteristics and outcome measures.

	No VTE N = 68	VTE N = 25
Baseline characteristics		
Age (years)	69.5 ± 11.0	67.4 ± 9.3
BMI (kg/m^2)	27.5 ± 6.1	28.6 ± 5.7
Gender (male)	36 (52.9%)	19 (76.0%)
Co-morbidities		
Smoking	3 (4.4%)	1 (4.0%)
Rheumatological disease	7 (10.3%)	1 (4.0%)
Obesity	21 (30.9%)	10 (40.0%)
Arterial hypertension	45 (66.2%)	12 (58.0%)
Diabetes	25 (36.8%)	6 (24.0%)
Outcome measures		
Pneumonia (including VAP)	38 (55.9%)	24 (96.0%)
Bacteremia	12 (17.6%)	16 (64.0%)
Catheter-related bloodstream infection	36 (52.9%)	24 (96.0%)
LOS ICU (days)	12.4 ± 10.4	36.2 ± 23.2
LOS hospital (days)	22.8 ± 18.9	49.7 ± 28.4
ICU mortality	22 (32.4%)	7 (28.0%)
Invasive mechanical ventilation	30 (44.2%)	22 (88.0%)

Data are presented as mean ± SD or frequencies (%).

Windows.

2. Results

A total of 116 COVID-19+ patients admitted to the ICU from 13th of March until 17th of October 2020 were included in the study. 23 patients were excluded for different reasons, i.e. not meeting the inclusion criteria (n = 11) [ICU admission due to neurological trauma (n = 2), diabetic ketoacidosis (n = 1), complication after surgery (n = 6) or negative COVID-19 test (n = 2)], no medical records (n = 10), other reason (n = 2), leaving 93 patients being analyzed. Baseline characteristics and outcome measures were shown in Table 1.

25 patients (26.80%) developed one or more VTE (1 VTE: n = 17, 2 VTE: n = 4 and 3 VTE: n = 4) with 23 patients suffering from a DVT whereas 2 patients suffered from a DVT with a PE.

64 patients (68.1%) suffered from at least 1 bacterial infection (catheter-related bloodstream infection, VAT or bacteremia) while 30 patients (31.9%) had no bacterial infection. We observed a correlation between the presence of VTE and the number of bacterial co-infection episodes (no VTE = 1.74 vs VTE = 5.48, p < 0.0001) (Fig. 1A). Furthermore, a correlation between the number of VTE locations (i.e. the inferior caval vein, iliac, femoral, popliteal, jugular, subclavian, brachial veins and/or pulmonary embolism) and the number of bacterial episodes was also found (Spearman correlation r = 0.53, p < 0.0001) (Fig. 1B).

3. Discussion

In this cohort study including 116 consecutive patients admitted to the ICU with severe SARS-CoV-2 infection, the following main observations were made: first, we found a strong correlation between both the presence of VTE and the number of VTE locations with the number of bacterial co-infection episodes, including pneumonia, bacteremia and catheter-related bloodstream infections in COVID-19 ICU patients. Second, patients diagnosed with VTE are at higher risk of suffering from multiple bacterial co-infections.

These observations may suggest the existence of a complex relationship between thrombosis risk and bacterial co-infections in COVID-19 ICU patients. It has been well-recognized that both viral and bacterial infections may be strong VTE triggers [9]. The temporal one-way relationship between the occurrence of an infection following colorectal surgery and the subsequent development of VTE has been proven [5]. However, to our knowledge, this is the first paper to describe a superimposed clear association between bacterial co-infection in COVID-19 ICU patients and thrombosis risk. Multiple mechanisms by which infection-mediated thrombosis is induced have been described. Viral and bacterial infection models to explain thrombosis during infection differ significantly and can be grouped into mechanisms concerning an infection-induced hypercoagulable state with increased systematic diffuse thrombosis or micro thrombosis formation [9] and mechanisms resulting in septic thrombophlebitis (i.e. direct thrombosis of a vein adjacent to the site of a primarily non-vascular bacterial infection) [10]. This may explain our observation of a superimposed thrombosis risk in patients who suffer from both severe viral infection and bacterial co-infection [9]. Another explanation of this observed superimposed thrombosis risk might be that patients with bacterial co-infections are more likely to be mechanically ventilated and thus sedated and

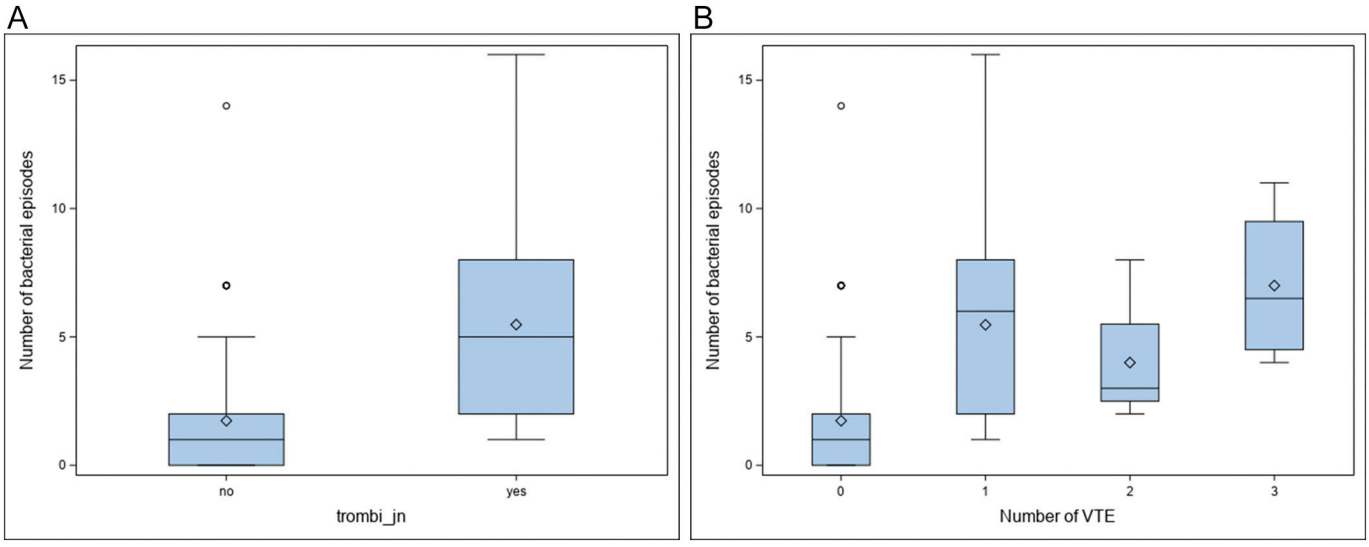

Fig. 1. The number of bacterial co-infection episodes correlates with the presence of VTE (A) and the number of VTE locations (B).
Patients suffering from VTE have a higher risk of developing bacteremia (OR = 7.85 (95% CI 2.83–21.80), p < 0.0001), pneumonia (including VAP) (OR = 12.94 (95% CI 2.25–74.35), p = 0.004) or catheter-related bloodstream infection (OR = 6.65 (95% CI 2.00–22.00), p = 0.002). After the incorporation of age, gender, BMI and invasive mechanical ventilation in the multivariate logistic model, these associations remain significant, i.e. bacteremia (OR = 8.56 (2.26, 32.44), p < 0.01), pneumonia (including VAP) (OR = 6.92 (1.11, 43.21), p = 0.03) and catheter-related bloodstream infection (OR = 6.87 (1.44, 32.69), p = 0.01).

immobilized. Indeed, a bidirectional relation exists between acute infection and immobilization, and both are triggers for VTE [4]. However, after correction for age, gender, BMI and invasive mechanical ventilation in the multivariate models, the associations between the 3 types of bacterial co-infection and thrombosis risk remained strongly significant. The observation that the vast majority of VTEs described were not local, e.g. PEs which could be expected in hospitalized patients due to pneumonia a, but DVTs, which is in contradiction with previous literature [11], might suggest that the mechanism responsible for the increased risk is systemic.

A second more controversial hypothesis to explain these results might be that COVID-19 ICU patients suffering from VTE are more at risk to develop bacterial co-infections (i.e. reverse causation), for instance: simply by prolonging hospitalization. The formation of thrombi stimulated by a COVID-19 infection might also create a perfect breeding ground for bacteria [12]. A thrombus can be infected via a distant, typically unidentified source of bacteremia and the poor antibiotic penetration of large size thrombi carry the risk of recurrent episodes of bacteremia [12]. In line with this hypothesis might micro-embolization of thrombi in the pulmonary vascular bed also explain the higher incidence of pneumonia in COVID-19 patients with VTE.

Finally, a third bystander may also cause both VTE and bacterial coinfections. For instance, a more severe COVID-19 disease or pre-existing comorbidities may independently increase the risk of both bacterial infection and VTE.

This study contains some limitations. First, the exact timing of diagnosis of VTE and bacterial co-infection episodes was not recorded. Therefore, we cannot draw firm conclusions regarding the temporal association between bacterial co-infections and VTE formation. Second, pulmonary embolisms were not systematically screened, potentially underestimating the presence of thrombo-embolic events. Finally, the mono-centric design of this study may limit the generalizability of these results.

In conclusion, our study suggests that, independently from the causal relationship between SARS-CoV-2 and elevated thrombosis risk, a superimposed clear association between bacterial co-infection and thrombosis risk is present in patients with a severe COVID-19 infection admitted to the ICU.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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