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Letter to the Editor

Intermediate dose thromboprophylaxis in SARS-CoV-2 related venous thrombo embolism

SARS-CoV-2 illness is associated with both pulmonary and extra pulmonary complications with hypoxemia being a marker of severity [1]. Evidence has shown an increase in venous thromboembolism (VTE) events both in intensive care unit (ICU) and non-ICU populations attributed to a multifactorial pathophysiological process [2,3]. Proximal disease related to true embolic event, distal disease representing thrombi related to the underlying inflammatory lung disease [4] and post-mortem data suggesting a possible role of small vessel micro thrombi contributes to the disease burden [5]. Coagulation abnormalities are common and an elevated D-Dimer level at admission is a marker of poor outcome and in hospital mortality [6]. Despite the increased prevalence of VTE there is a paucity of data to guide the clinicians about the optimal approach in identifying patients who may benefit from intermediate dose. Intermediate dose thromboprophylaxis is recommended for patients requiring high-flow oxygenation and invasive ventilation in critical care domain in many expert centres [7]. As per the British Thoracic Society guidance it is not possible to advocate any particular approach and suggests implementing local protocols for risk stratification [8]. Clinical data regarding the associated bleeding complications in intermediate thromboprophylaxis is lacking.

We evaluated the VTE event rate, admission to critical care and intermediate thromboprophylaxis dose related bleeding complication rate in SARS-CoV-2 positive and negative patients**.** This was a single centre retrospective evaluation and SARS-CoV-2 patients on admission were clinically risk stratified and appropriate LMWH thromboprophylaxis was considered. All patients who were on prior anticoagulation either with Warfarin or DOAC (Direct oral anticoagulants) for any medical reasons were switched to full dose LMWH anticoagulation and were excluded from the final analysis. Patients with clinical symptoms as defined by the World Health Organisation along with admission chest radiograph suggestive of SARS-COV-2 and with a positive naso-oropharyngeal swab were classified as SARS-COV-2 positive cohort. The sensitivity of the naso-oropharyngeal swab for SARS-CoV-2 is between 71-98% and thus patients with a high degree of clinical suspicion and or if the admission chest radiograph was suggestive of SARS-CoV-2 despite two negative naso-oropharyngeal swabs were classified as clinical SARS-CoV-2 and were treated similar to SARS-CoV-2 positive cohort. Patients with no clinical suspicion, normal admission chest radiograph and with a negative naso-oropharyngeal swab were classified as SARS-CoV-2 negative cohort. The appropriate thromboprophylaxis dose was considered following a locally agreed risk assessment based on naso pharyngeal swab result, mobility on admission, thrombosis and bleeding risk. Patients deemed low risk for VTE were treated with standard LMWH prophylaxis, once daily dose (Tinzaparin, Leo laboratories, 4500 Units) or Enoxaparin (Sanofi, 20-60 mg). Intermediate LMWH prophylaxis was considered in SARS-CoV-2 positive patients only who were found to be high risk for a VTE. Additional risk factors for considering intermediate LMWH prophylaxis included the need for oxygen therapy, previous history of VTE or arterial embolic disease, active cancer, or chemotherapy/radiotherapy within the last 6 months, any prothrombotic medical conditions, BMI >30 on admission and admission to critical care. Patients who were pregnant and those in the puerperium phase were excluded from this regime due to perceived bleeding risks. The dose was twice daily and was dependent on creatinine clearance (> 30 ml/min for Tinzaparin and < 30 ml/min for Enoxaparin) and actual body weight. The regimen was subsequently altered to standard dose following VTE exclusion and thromboprophylaxis was ceased in all patients at the time of discharge. Full dose anticoagulation was considered in all patients who had a confirmed VTE based on either a CTPA (Computerised tomographic Pulmonary Angiogram) or a Doppler ultrasound or in patients who were clinically unstable for radiological evaluation. Statistical analysis were carried out with Graph pad Prism, version-8; mean (SD), median (IQR), unpaired t-tests, chi square test were used and P value of < 0.05 was considered statistically significant.

502 (age; 65 +/- 19 years, females; 56%) patients with suspected SARS-CoV-2 underwent either a CTPA or a Doppler of the upper or the lower limb. SARS-CoV-2 positive patients had a significantly higher incidence of VTE as compared to patients who were negative (35.9% v/s 13.9%, P = < 0.0001, OR = 3.47, 95% CI; 2.2-5.4). The D-Dimer on admission was significantly higher in the SARS-CoV-2 positive patients with VTE as compared to SARS-CoV-2 negative patients with VTE (median D-Dimer value; 2.09 mg/L versus 1.2, P = 0.03). SARS-CoV-2 positive patients with a VTE episode were more likely to need critical care admission as compared to patients who were negative for SARS-CoV-2 (18% versus 4.5%, P = 0.03, OR = 4.84, 95% CI; 1-23) (Fig. 1).

Majority of patients in both the groups had a CTPA (82%, n = 140, SARS-CoV-2 positive v/s 60%, n = 199, SARS-CoV-2 negative) and Doppler ultrasound in (18%, n = 31, SARS-CoV-2 positive v/s 40%, n = 132, SARS-CoV-2 negative) respectively. In patients receiving intermediate dose of thromboprophylaxis bleeding complications rate was 1.7% (2/118, non-traumatic subdural haematoma, non-traumatic urethral bleeding and both were managed conservatively) and these patients were SARS-CoV-2 positive with a confirmed diagnosis of VTE. Both patients were initially treated with intermediate dose of LMWH before switching over to full dose Apixaban following the CTPA results. No patients were thrombolysed. Enoxaparin 60 mg OD was considered in patients with a weight of more than 150 kgs, but no patient received this dose.

Appropriate management of VTE in SARS-CoV-2 remains a challenge with on-going debate about the issue of optimal thromboprophylaxis. The association of VTE is not specific to SARS-CoV-2 and this phenomenon previously has been seen during the H1N1 outbreak [9]. Many pathophysiological processes have been postulated and are likely to be a

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summation of intense endothelial inflammation leading to heparin resistance, altered pulmonary flow leading to worsening gas exchange and transition from a DVT to PE. VTE event rate is significantly higher in SARS-CoV-2 and these patients should be considered as high risk group and appropriate risk assessment at admission should be implemented. The VTE event rate in patients who were SARS-CoV-2 negative was similar to our local practice which was audited during the pre SARS-COV-2 period. Coagulopathy seen in SARS-CoV-2 is associated with marked fibrin formation, leading to very high D-dimer levels with lungs being the most likely site of fibrin formation. Patients with SARS-CoV-2 positive often have a higher D-Dimer assay but a cut off for deciding about CTPA can be challenging due to low specificity associated with D-Dimer levels. Recent evidence suggests a cut off of more than 2500 (2.5 mg) is an independent predictor for PE in severe SARS-CoV-2 illness [10] and our data is close to this finding. Thus patients with higher D-Dimer assay at admission should be considered as high risk and may benefit from intermediate dose of thromboprophylaxis. The practice of intermediate thromboprophylaxis did not transform to a high incidence of bleeding complications. The bleeding complications were trivial and did not need any specific intervention. No complications were seen with LMWH but following a switch to DOAC. None of the patients were initiated on LMWH prophylaxis prior to hospital admission.

Our study had limitations; firstly, the gold standard diagnostic method of infection confirmation was the reverse- transcription polymerase chain reaction (RT-PCR). As the pandemic swept across the UK and hospital caseloads surged we faced many challenges in the beginning- clinical sampling techniques; variations in viral load, manufacturer test kit sensitivity and staff redeployment. Importantly, bronchoscopy was considered as a high risk aerosol generation procedure and many patients were unstable for this intervention. In order to reduce the infection spread we opted for a pragmatic approach to treat patients with high degree of clinical suspicion (symptoms + abnormal radiograph + unexplained lymphopenia) as clinical SARS-CoV2 despite

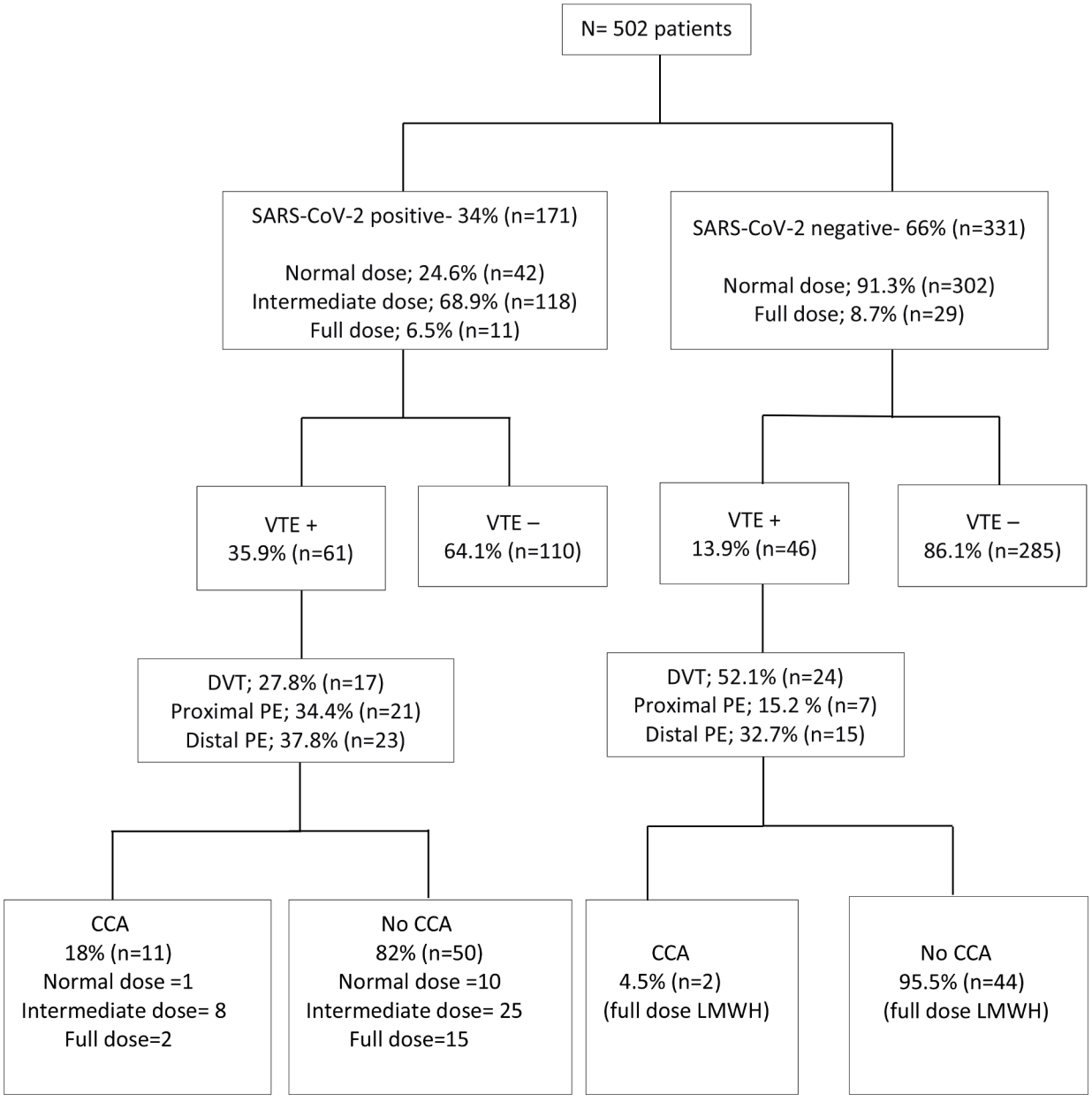

Fig. 1. Consort diagram-1, showing the VTE event rate between SARS-CoV-2 positive and negative patients Proximal PE = Saddle/lobar/bilateral, Distal PE = Segmental/sub segmental, CCA = Critical Care Admission

2 negative swabs. It is to be noted that these patients constituted a minority (4%, n = 7/171). Secondly despite clinical risk assessment not all patients had further radiological investigations especially the asymptomatic cohort and patients needing ICU support who were not clinically stable. Strict infection control measures that were aimed at containing patient movement in order to minimise nosocomial and cross infection spread and also due to capacity issues affecting our stretched radiology services, clinicians may have opted to clinically treat with full dose anticoagulation which may have underestimated the true VTE event rate. Doppler ultrasonography was done on the same day at the bed side by a certified sonographer. On the contrary the median duration from admission to CTPA was 3 days (range; 2-6) in SARS-CoV-2 positive patients and this was largely dependent on patient's clinical stability for transfer to the radiology department. The median duration in SARS-CoV-2 negative patients was 2 day (range; 1-3).

In conclusion, SARS-CoV-2 positive patients with a higher D-Dimer at admission are more likely to have a VTE and are more likely to need critical care support. Intermediate thromboprophylaxis is probably safe with low bleeding risks but needs further studies to confirm this. SARS-CoV-2 positive patients should be considered as "high risk for VTE" and intermediate thromboprophylaxis should be considered in these patients. In the absence of RCTs we cannot provide firm conclusions on the recommended dosage.

Declaration of Competing Interest

All authors declare no conflict of interest

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