Incidence and significance of venous thromboembolism in critically ill pulmonary tuberculosis patients

To the Editor:

Venous thromboembolism (VTE) has not been reported to be a contributor to the poor outcomes in pulmonary tuberculosis (PTB) patients requiring intensive care [1]. Haemostatic changes that favour the development of VTE, however, are well documented in PTB [2–4]; and, compared with patients without active tuberculosis (TB), those with active TB are known to be at increased risk for VTE [5]. We have been impressed by the frequency with which clinically diagnosed VTE, both deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), are present in critically ill PTB patients (where "PTB" refers to both adult-type pulmonary TB and miliary/disseminated TB), with critical illness being either the cause or effect of VTE. Herein, we document this high frequency and raise awareness of this potentially serious complication.

We conducted a retrospective observational cohort study of all adult (age >17 years) smear-positive, culture-positive PTB patients admitted over an 11-year period, beginning on 1 January, 2006, to the University of Alberta Hospital, the TB referral hospital for the city of Edmonton and all of rural Alberta, Canada. In Alberta, smear-positive PTB patients are routinely admitted to hospital; those not diagnosed with VTE on admission are prescribed DVT prophylaxis (standard dose low molecular weight heparin). We used administrative and radiology databases to determine which PTB patients required intensive care unit (ICU) admission and which were investigated for DVT or PTE. DVT were diagnosed by compression ultrasonography; PTE by helical computerised tomographic pulmonary angiography (CTPA).

Demographic and clinical characteristics of PTB patients who did or did not require ICU and admission P/F ratios (arterial oxygen tension (P_{aO_2})/inspiratory oxygen fraction (F_{IO_2})) in ICU-requiring PTB cases who did or did not have VTE were compared. The timing of VTE investigations relative to the date of diagnosis of PTB (the start date of anti-TB drug treatment) and the outcomes of those investigations were recorded. Each VTE event was described; for patients with PTE this included having each CTPA re-read by an experienced, university-based chest radiologist who confirmed the event and documented the anatomical location of PTE relative to the anatomical location of PTB. VTE diagnosed at the time of or up to 30 days before the diagnosis of PTB were considered prevalent events; VTE diagnosed after the diagnosis of PTB but before discharge from hospital were considered incident events. TB-related death (occurring during treatment of active disease, where TB was considered the primary or contributory cause of death) was compared in VTE-tested PTB patients with and without VTE. Univariate analysis was performed for categorical data using Pearson's Chi-squared test or Fisher's exact test, as appropriate. A two-tailed p-value <0.05 was taken as statistically significant. Appropriate institutional ethics approval was obtained.

Over the study years, 240 PTB patients were admitted to hospital; of these, 20 (8.3%) required intensive care and 10 (4.2%) were diagnosed with VTE (figure 1). 19 of the 20 ICU admissions were for respiratory insufficiency; one was for hypotension requiring vasopressor support. Patients requiring intensive care were older (>64 years) (45.0% *versus* 19.1%, p=0.01) and more likely to have miliary/disseminated TB (50% *versus* 13.6%, p=0.0002), to have longer hospital lengths of stay (median (interquartile range) days 39.5 (17.3–74.3) *versus* 23.0 (14.0–38.8), p=0.03), and to die in hospital (20.0% *versus* 1.8%, p=0.0005).

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Venous thromboembolism (VTE) is common in critically ill pulmonary tuberculosis (PTB) patients despite thromboprophylaxis. Clinicians need to be aware of the association between PTB, VTE and critical illness as it has management and outcome implications. https://bit.ly/2Ns7JWZ

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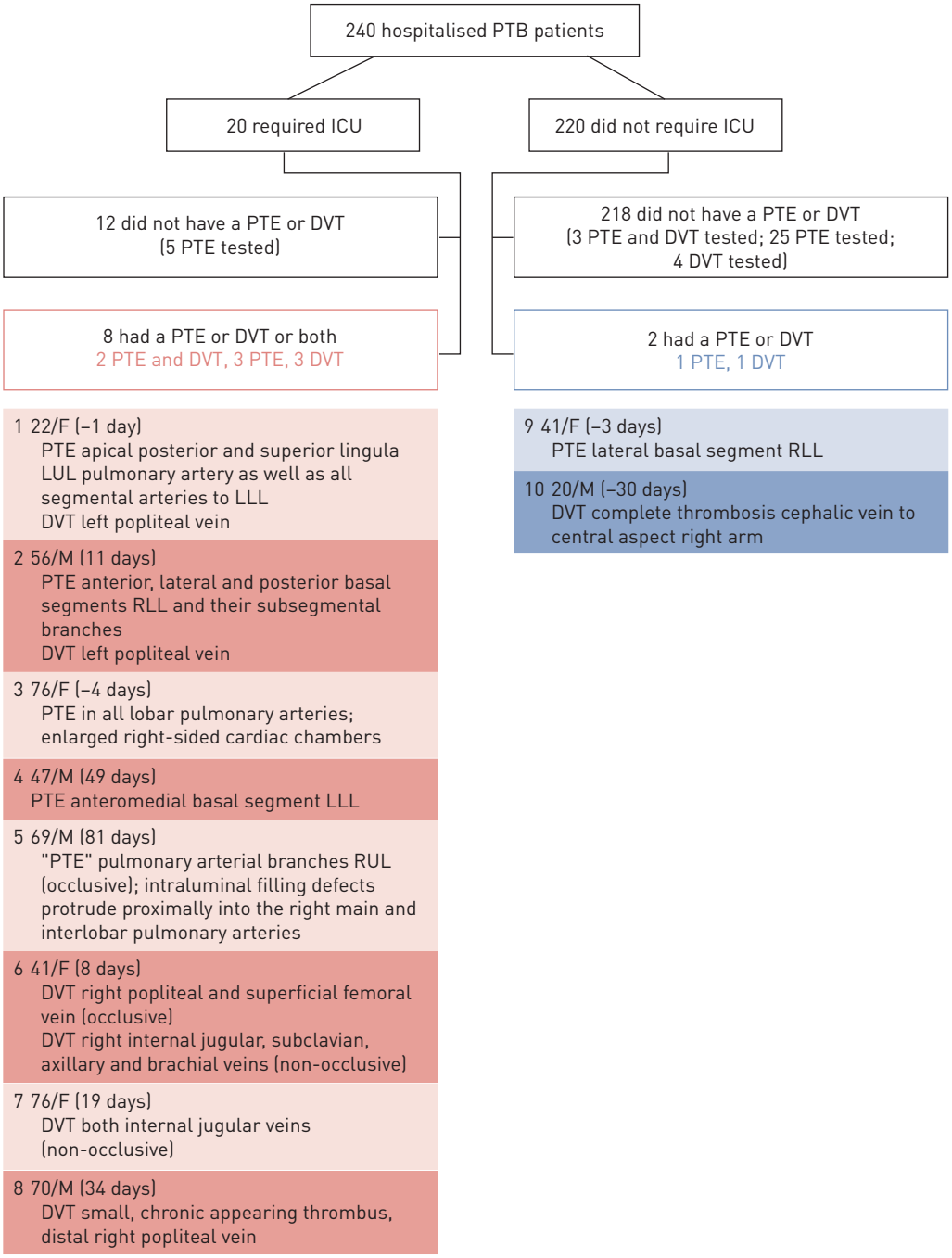

FIGURE 1 Hospitalised pulmonary tuberculosis (PTB) patients: individual intensive care unit (ICU) and venous thromboembolism (VTE) histories. For individual patients their age, in years, and sex at diagnosis is given, followed by numbers in brackets indicating the number of days between the diagnosis of PTB and VTE. In four patients the diagnosis of VTE preceded the diagnosis of PTB; in six patients it followed the diagnosis of PTB. In two patients (#4 and #7), the date of admission to ICU (and the start date of deep vein thrombosis (DVT) prophylaxis) preceded the date of diagnosis of PTB. In these patients the days reported are those from ICU admission to VTE. PTE: pulmonary thromboembolism; M: male; F: female; LUL: left upper lobe; LLL: left lower lobe; RLL: right lower lobe; RUL: right upper lobe.

They did not differ by sex, population group, HIV status, or drug resistance pattern (data not shown). ICU patients with VTE were more likely than those without to have a severe P/F ratio (<100) on admission (50.0% *versus* 0.0%, p=0.03; data not shown). In four patients the diagnosis of VTE was made at the time of or up to 30 days before the diagnosis of PTB; in two of these four, one with DVT and PTE and another with PTE alone, the VTE and PTB diagnoses and ICU admission followed in rapid succession, with VTE judged to be a major contributor to the need for intensive care (patients #1 and #3 in figure 1).

In six patients the diagnosis of VTE was made after the diagnosis of PTB and while the patient was either in the ICU or after discharge from the ICU but before discharge from hospital. These patients had all been placed on DVT prophylaxis for a median of 27 days, range 8 to 81 days (see time from diagnosis of PTB to VTE in figure 1). No incident VTE occurred in hospitalised PTB patients that did not require intensive care. Among the six patients experiencing a PTE, the clot had gone to relatively non-TB-diseased lung in four, to both TB-diseased and non-TB-diseased lung in one, and to TB-diseased lung alone in one. In this last patient (#5 in figure 1) the clot was favoured to represent *in-situ* thrombosis over PTE. The prevalence of VTE was 1.7% (95% CI 0.6%–4.2%); the incidence of VTE in hospitalised PTB patients who required intensive care was 33.3% (95% CI 16.3%–56.3%), or 27.8% if the patient favoured to have *in-situ* thrombosis, and not PTE, was discounted.

Amongst VTE-tested PTB patients (n=47), a TB-related death was reported in six out of 10 (60.0%) of those with and four out of 37 (10.8%) of those without VTE (OR 12.4 (95% CI 2.4–63.6), p=0.003) (data not shown).

The remarkably high incidence of clinically diagnosed VTE reported herein is much higher than the 1–2% incidence reported in critically ill medical-surgical patients in general [6]. And, while DVT prophylaxis prevented VTE in the 218 patients who were not admitted to ICU (and not already diagnosed with VTE), it did not prevent VTE in six of the 18 patients who were admitted to ICU (and not already diagnosed with VTE). Thus, the hypercoagulable state of PTB appeared to be manageable with routine DVT prophylaxis in all but those requiring ICU. PTB patients requiring ICU were similar to those reported elsewhere in Canada [7]. Presumably their critical-illness-related risk of VTE, attributed to immobility, neuromuscular blockade, vasopressors, sepsis and central venous catheterisation, and/or critical-illness-related failure to absorb DVT prophylaxis, attributed to decreased subcutaneous perfusion secondary to oedema/vasopressors, rendered routine DVT prophylaxis inadequate [8, 9]. In unadjusted analysis, VTE carried a significant mortality risk.

Independent of ICU admission, PTB patients with PTE are known to have a higher pulmonary embolism severity index (PESI) and more frequently have a high PESI class than control non-PTB patients with unprovoked PTE [10]. In this regard it is noteworthy that the pathophysiologic defect in uncomplicated PTB is one in which ventilation and perfusion to diseased lung is reduced in parallel and gas exchange is relatively well preserved [11]. This would predict that PTE, if they occur, are more likely to migrate to relatively normal lung and have a greater deleterious effect on gas exchange (increase in physiological dead space) the smaller the volume of normal lung remaining. With the exception of one patient, who was favoured to have *in-situ* thrombosis, PTE had migrated to relatively non-TB-diseased lung; upon admission to ICU patients with VTE were more likely, than those without VTE, to have severe P_{aO_2}/F_{IO_2} ratios. The occurrence of PTE, if associated with an elevated pulmonary artery pressure, would also predict that Rasmussen aneurysms, if present, would be more likely to rupture, further compromising gas exchange. They are present in 4% of chronic cavitary PTB patients [12].

The incidence, morbidity and mortality data presented here strongly suggest the need for a high index of suspicion for VTE in PTB patients requiring intensive care. Until alternative preventive measures such as high dose prophylaxis are proven to be effective [13] and given that lower limb DVT are the primary source of PTE [14], the systematic screening of ICU-requiring PTB patients for DVT may be warranted [15].

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