Original Article

Pulmonary Embolism following Complex Trauma: UK MTC Observational Study

Short Title: Pulmonary Embolism in a UK MTC

Thomas E Glover[1] MB BChir.	thomasglover52@gmail.com
Joanna E Sumpter[1] BM BCh	joanna.sumpter@gmail.com
Ari Ercole[1,2] PhD	ae105@cam.ac.uk
Virginia FJ Newcombe[1,2] PhD	vfjn2@wbic.cam.ac.uk
Andrea Lavinio MD[1]	andrea.lavinio@addenbrookes.nhs.uk
Andrew Carrothers[3] MA	andrew.carrothers@addenbrookes.nhs.uk
David K Menon[1,2] PhD	dkm13@cam.ac.uk
Ronan O'Leary[1] PhD	mail@ronanoleary.net

1. Neurosciences and Trauma Critical Care Unit
   Addenbrooke's Hospital
   Cambridge University Hospitals
   Cambridge CB2 0QQ
   UK

2. University of Cambridge Division of Anaesthesia
   Box 93, Addenbrooke's Hospital,
   Cambridge CB2 0QQ
   UK

3. Orthopaedic and Trauma Unit
   Addenbrooke's Hospital
   Cambridge University Hospitals
   Cambridge CB2 0QQ
   UK

Correspondence: Dr Ronan O'Leary. Neurosciences and Trauma Critical Care Unit, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ. +44 122 324 5151. mail@ronanoleary.net

Word Count: 2768

ABSTRACT

Purpose: To describe the natural history of pulmonary embolism in a critically ill UK major trauma centre (MTC) patient cohort.

Methods: A retrospective study of all critically ill trauma patients admitted to the East of England MTC using the Trauma and Audit Research Network (TARN) database, electronic medical records, and our Picture Archiving and Communication System (PACS) was conducted. Data describing demographics, the nature and extent of injuries, process of care, timing of PE prophylaxis and tranexamic acid (TXA) administration and CT scanner type were collected. PE timing was divided into immediate (diagnosed on initial trauma scan), early (within 72 hours of admission but not present initially) and late (diagnosed after 72 hours). Data were analysed using standard statistical tests.

Results: 1039 (of 2746) patients were admitted to a critical care environment at the East of England MTC from 1st November 2014 to 1st May 2017. Forty-eight patients (4.6%) were diagnosed with PE during admission with 14 immediate PEs (1.3%). Of 32.1% patients given TXA, 6.3% developed PE ($p = 0.08$). There was no significant difference in detection of sub-segmental PE (SSPE) in 64-slice and 128-slice CT scanners ($p = 0.81$).

Conclusions: This is the largest study of the incidence of PE in UK MTC patients and describes the greatest number of immediate PEs in a civilian trauma population to date. Immediate PEs are a rare phenomenon whose clinical importance remains unclear. Tranexamic acid was not associated with a significant increase in PE incidence following its introduction into the UK trauma care system. Increasing CT scanner density from 64 to 128 rows does not appear to increase SSPE detection.

Keywords: pulmonary embolism, tranexamic acid, major trauma.

WHAT THIS STUDY ADDS

What is already known on this subject: The natural history of pulmonary embolus (PE) in the complex trauma population is poorly characterised particularly since the implementation of nationally co-ordinated major trauma systems. Specifically, immediate PE - PE diagnosed on initial trauma CT scan - is a vaguely desribed phenomenon with uncertain aetiology and clinical significance. Furthermore, the consequences of system wide changes to trauma care, such as the mandatory national introduction of tranexamic acid (TXA), have yet to be studied with the respect to PE. Finally, improvements in imaging and the ubiquity of total body CT immediately after trauma may increase the rate of detection of PE, particularly sub segmental PE, and therefore the inappropriate use of therapeutic anticoagulation.

What this study adds: This study population describes the greatest reported incidence of immediate PEs in a large complex trauma population presenting to a UK major trauma centre - 4.6 % with approximately one third being immediate and the remainder presenting after 72 hours. The association of immediate PE with severe chest trauma may suggest that these lesions are in fact de novo thrombi forming in the lungs rather than embolic phenomenon, therapeutic anticoagulation may be unwarranted. These data support the evidence that tranexamic acid does not increase the rate of PE. Finally, PEs were not diagnosed more frequently due to improvements in CT detector technology.

INTRODUCTION

Venous thromboembolism (VTE) represents a substantial burden of disease following trauma.[1, 2] Contemporary management of trauma has evolved significantly in recent years with increased use of computed tomography (CT) imaging with contrast and changes to clinical care, for example early use of blood products, management of trauma-induced coagulopathy, and antifibrinolytic administration. However, the true incidence and characteristics of trauma associated VTE, particularly PE, has not been established as trauma care has evolved. For example, a recent systematic review of predominantly US trauma patient cohorts found a large range in the reported incidence of PE, 0.35 to 24%,[3] which does not sit well with current experience, particularly in the UK trauma centre population.

Classic teaching states that the majority of PEs occur within the first week of injury with up to 25% of PEs occurring within the first 4 days.[4,5] However, many of these studies predate the routine use of pharmacological VTE prophylaxis or were conducted prior to the introduction of nationally co-ordinated trauma systems. Furthermore, later refinements of these trauma systems, such as the inclusion of mandatory tranexamic acid (TXA), have yet to be studied with respect to their impact on VTE.

There are further gaps in our knowledge in the pathophysiological landscape of VTE and PE following trauma. For example, PEs are thought to originate from thrombi in the extremities before migrating to the lungs as emboli[5,6] however a number of studies have described PE without deep vein thrombosis (DVT).[7-9] Intriguingly, several studies have reported the presence of thrombus in the pulmonary circulation within the first few hours of traumatic injury, which has given rise to the concept of *immediate* PE (or *de novo* intrapulmonary thrombus) postulated to exist separately from classical PE.[10,11] The role for anticoagulation when PEs

present in this way, particularly in the presence of co-existent traumatic haemorrhagic lesions, is unknown.

The recent development of the UK trauma system provides a useful research substrate to describe complex-trauma associated VTE, particularly outside a non-US healthcare system.[12] Moreover, the introduction of tranexamic acid administration as standard practice in early trauma care throughout the National Health Service (NHS) also offers an unique opportunities to explore the relationship between TXA and VTE in this population. We have therefore examined the natural history of PE in all adult complex trauma patients presenting to a UK Major Trauma Centre (MTC) and the association between PE and administration of TXA. Additionally, given the concern that an increased detection of sub-segmental PE (SSPE) may occur due to increased sensitivity of modern multi-detector CT scanners,[13] we have assessed the relationship between CT detector density and detection of SSPE.

METHODS

We conducted a retrospective study of consecutive patients aged 18 years and over admitted to the East of England Major Trauma Centre (MTC) at Addenbrooke's Hospital, Cambridge, UK between 1st November 2014 and 1st May 2017 (30 months) using data submitted to the Trauma Audit and Research Network (TARN) database,[14] local electronic patient records, and our digital radiology Picture Archiving and Communication System (PACS). The study was registered locally and approved as a service evaluation.

We used a pragmatic definition of admission to a critical care environment to determine severely injured trauma patients. Patient demographics, the nature and extent of injuries, Injury Severity Score (ISS), Abbreviated Injury Score (AIS), process of care, radiological findings, type of CT scanner, and timing of administration of TXA, and low molecular weight heparin (LMWH) were collected.

PE time of diagnosis was divided into immediate (diagnosed on initial trauma scan), early (within 72 hours of admission but not present on initial scan) and late (diagnosed from 72 hours to 6 weeks into admission).

CT scans were routinely performed in all trauma patients admitted to a critical care environment. CT scanners used included Siemens Somatom® Definition AS, AS+ and Flash models ranging from 64 to 128-row detectors, and in one case a Philips Brilliance-64® scanner in a peripheral hospital (64-row detector). Trauma patients were scanned with either a 64- or 128-row scanner depending on availability at the time of admission.

Data were analysed using standard statistical tests – Mann Whitney U, Fisher's Exact, and χ^2 Tests as appropriate. Statistical significance is presented without correction for multiple comparisons.

RESULTS

Patient Characteristics

Over the study period 2,746 trauma patients presented to the MTC of which 1,039 were admitted to a critical care environment (Figure 1 and Table 1). Vehicle collisions and falls accounted for the majority of patient admissions (88.5 %) with high energy mechanisms significantly over represented in the PE cohort. PE was defined as a filling defect within the pulmonary arterial system identified on CT imaging. Forty-eight patients (4.6 %) developed PE, of these, 14 (1.3% of total population, 29.1 % of those with PE) were diagnosed as having immediate PE, 8 (0.8% of total population, 16.7% of those with PE) had early PE, and 26 (2.5 % of total population, 54.2% of those with PE) were found to have late PE (time of diagnosis 4 - 44 days (Figure 2). The majority of PEs occurred after 72 hours of admission.

Table 1: Patient characteristics. AIS: abbreviated injury scale score; ISS: injury severity score; LOS: length of stay. Results presented as mean ± 95% confidence interval unless otherwise stated.

Variable	PE	No PE	P value
Number	48	991	
Age (years)	49.3 (± 5.0)	49.3 (± 1.2)	0.97
Sex (% male)	66.7	73.6	0.29
APACHE II	14	13.1	0.68
ISS	27.9 (± 3.5)	25.2 (± 0.7)	0.21
AIS head	1.9 (± 0.7)	2.4 (± 0.1)	0.23
AIS chest	2.5 (± 0.5)	1.8 (± 0.1)	<0.01
AIS pelvis	0.9 (± 0.4)	0.7 (± 0.1)	0.24
AIS limbs	1.8 (± 0.3)	1.1 (± 0.1)	<0.01
Mechanism			
High energy	40	698	0.05
Fall > 2m	8	186	
Vehicle incident	31	512	
Shooting	1	4	
Low energy	8	293	
Fall < 2m	8	177	
Stabbing	0	21	
Blow	0	66	
Crush	0	10	
ICU LOS (days)	14.4 (±3.5)	7.4 (± 0.6)	<0.01
Hospital LOS (days)	31.8 (± 6.2)	24.1 (± 1.7)	<0.01
Mortality (%)	18.7	14.5	0.42

Table 2: Patient characteristics by PE subgroup. AIS: abbreviated injury scale score; ISS: injury severity score; LOS: length of stay; PE: pulmonary embolism. Results presented as mean ± 95% confidence interval unless otherwise stated.

	Immediate PE	**Early PE**	**Late PE**
Number	14	8	26
Age (years)	47 (± 7.9)	42 (± 7.6)	53 (± 7.7)
Sex (% male)	64.3	67.5	69.2
APACHE II	14	14.3	14.2
ISS, median (range)	25 (9-45)	30 (22-50)	25 (8-59)
ISS > 15 (%)	85.7	87.5	84.6
AIS head	2.6 (± 1.3)	1.9 (± 1.8)	1.5 (± 0.3)
AIS chest	1.6 (± 0.9)	2.4 (± 1.5)	3.1 (± 0.5)
AIS pelvis	0.6 (± 0.6)	1.4 (± 1.1)	0.9 (± 0.6)
AIS limbs	1.9 (± 0.7)	1.9 (± 1.1)	1.7 (± 0.4)
LOS (days)	32.6 (± 15.5)	30.5 (± 11.6)	31.8 (± 7.5)
Mortality (%)	28.6	25.0	11.5

Figure 1: Study Population.

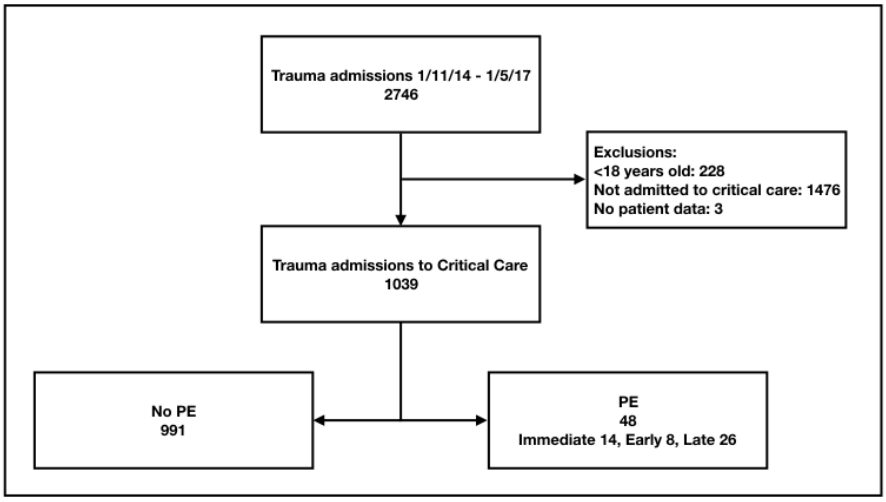
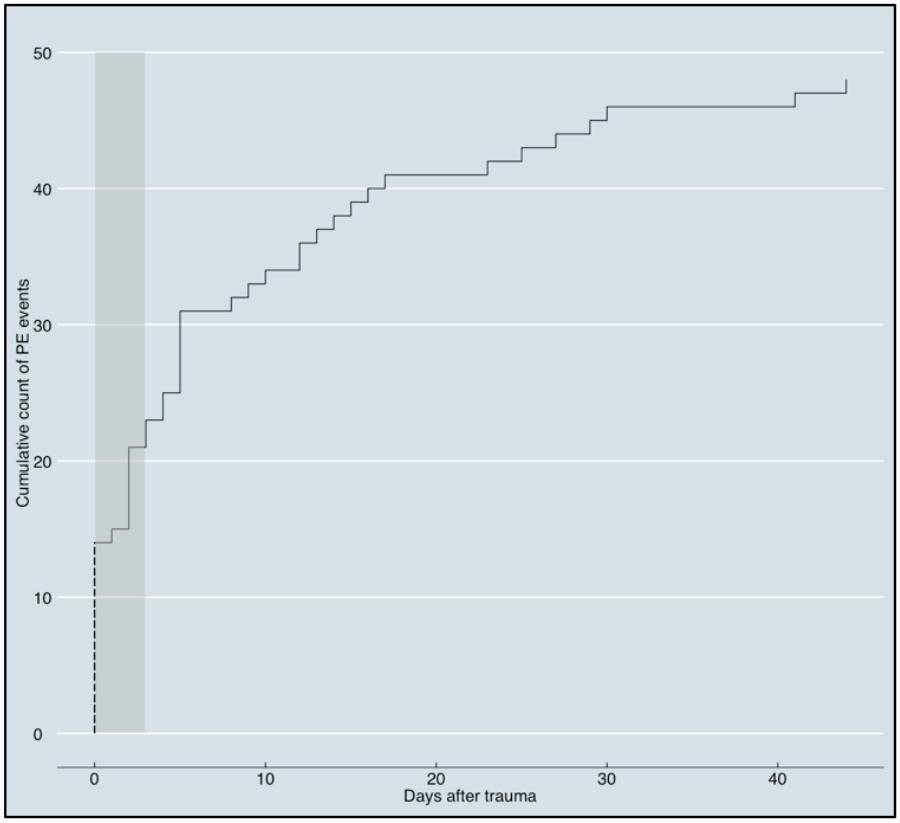


Figure 2: Cumulative distribution of early and late PEs in our UK MTC trauma population. The grey shaded area represents the first 72 hours following admission.



Immediate PE

Twelve of the 14 patients with immediate PE (85 %) had an initial trauma CT scan shortly after admission to the emergency department (< 2.6 hr following admission). The two remaining patients underwent emergency laparotomy prior to scan due to haemodynamic instability and had scans 5.2 hours and 24 hours following admission. Median ISS was 25 (range 9-45). Three patients (29 %) died within 24 hours of admission however none of these deaths were due to respiratory or cardiovascular failure. Seven patients had chest injuries, ten had limb injuries, while three had pelvic injuries. All but 3 sustained high-energy trauma. Only three patients underwent lower limb Doppler of which one was positive for DVT. The majority (n = 11) had more than one pulmonary thrombus on CT scan. Three patients had SSPE.

Early PE

Seven of the 8 patients with early PE had ISS>15 (median ISS 30, range 22-50) the remaining patient had an ISS value of 9. Chest and limb injuries were present in 5 patients, while 4 patients had pelvic injuries. There were two deaths but these were not attributable to cardiorespiratory failure. Two patients (25 %) had SSPE.

Late PE

Twenty-two of the 26 patients with late PE (85 %) had ISS>15, mean ISS 28 (95% CI 22.6 to 33.4), the remaining 4 patients had ISS value of 8-14. 22 had chest injuries, while 19 had limb injuries and 9 had pelvic injuries. Seven patients (26.9 %) had SSPEs.

Association with TXA administration

333 patients were given TXA either pre-hospital or immediately following admission to the Emergency Department. The patients who received TXA were younger, had more severe injuries overall and had significantly worse chest, pelvis and limb injuries than patients who had not received TXA but there was no significant difference in mortality (Table 3). Twenty-

one patients (6.3 %) developed PE in the TXA group compared to 27 in the no-TXA group (3.8 %), $p = 0.08$.

Table 3: TXA administration subgroup characteristics. AIS: abbreviated injury scale score; ISS: injury severity score; LOS: length of stay; PE: pulmonary embolism. Results presented as mean ± 95% confidence interval unless otherwise stated.

Variable	TXA	No TXA	P value
Number	333	706	
Age (years)	46.0 (± 2.0)	50.9 (± 1.4)	<0.01
Sex (% male)	75.7	72.1	0.22
APACHE II	13.0	13.3	0.62
Immediate PE (n, %)	7 (2.1%)	7 (1.0%)	0.15
Early PE (n, %)	5 (1.5%)	3 (0.4%)	0.11
Late PE (n, %)	9 (2.7%)	17 (2.4%)	0.77
Total PE (n, %)	21 (6.3%)	27 (3.8%)	0.08
ISS	28.3 (± 1.3)	23.8 (± 0.8)	<0.01
AIS head	2.1 (± 0.2)	2.5 (± 0.2)	<0.01
AIS chest	2.4 (± 0.2)	1.5 (± 0.1)	<0.01
AIS pelvis	1.0 (± 0.2)	0.5 (± 0.1)	<0.01
AIS limbs	1.6 (± 0.2)	0.9 (± 0.1)	<0.01
LOS (days)	27.8 (± 3.2)	22.9 (± 1.8)	<0.01
Mortality (%)	14.1	15.0	0.70

Timing of administration of LMWH in immediate PE patients

Of the 11 immediate PE patients alive after 72 hours of admission, 7 (64 %) received therapeutic (t)LMWH within 72 hours. In this group 1 patient developed large bilateral PEs on day 14, this patient had received prophylactic (p)LMWH on day 1 of admission and been upgraded to tLMWH on day 13.

In the group of 4 patients who did not receive tLMWH within 72h of diagnosis pharmacological VTE treatment was commenced 9 and 45 days following admission, apart from one patient who did not receive therapeutic anticoagulation during their hospital admission.

Other than the case described above there were no other immediate PE patients who developed subsequent PE. There were no fatalities.

CT SSPE sensitivity

The majority of patients with PE (83.3 %) were diagnosed using 128-row CT scanners, the remainder diagnosed by 64-row scanner. There was a non-significant difference in detection of SSPEs, 10/41 (24.3 %) patients diagnosed using 128-row scanners had SSPE, while 2/7 (29 %) patients diagnosed using 64-row scanners had SSPE ($p = 0.81$).

DISCUSSION

This study is the first to describe the natural history of PE in an UK MTC, the first since the introduction of mandatory TXA into any nationally co-ordinated civilian trauma system and the first, to our knowledge, to describe the incidence of immediate as a separate clinical entity, early, and late PEs within a critically ill civilian trauma cohort. We report an overall incidence of PE of 48/1039 (4.6%), of which 14 (29.1% of all PEs) were immediate PEs, detected on admission. TXA was administered to selected patients due to gradual integration of TXA into our MTN protocol during the study period. Patients treated with TXA were younger, had more severe injuries and longer admissions. A higher but not statistically significant rate of PEs was observed in the TXA-treated cohort. Finally, we asked whether increasing CT detector density would increase the number of SSPEs diagnosed and subsequently increase the risk of over-treatment of PE in complex trauma patients. In this population, no significant difference in the detection of SSPE was identified between 64-slice and 128-slice scanners.

This study reports the highest incidence of immediate PEs in a civilian trauma population and almost 2.5 times the incidence recorded in arguably the most similar published study,[15]. The remaining PEs in this cohort presented over the following 6 weeks with the majority presenting after 72 hours. This is similar to previous studies with comparable trauma populations, although in those studies TXA was not routinely administered.[16]

Immediate PE in trauma remains a surprisingly rare phenomenon, the aetiology and clinical significance of which remain unclear. Several studies have suggested that immediate PE may be not be related to DVT and may exist as a separate entity that arises in the lungs *de novo* following traumatic injury.[9-11] In keeping with this theory, most immediate PEs in our study,

as in other reports [17, 18] were diagnosed within hours of injury, with minimal time for a DVT to form and generate emboli. Chest and limb injuries were more frequently associated with immediate PE than pelvic injuries, which does not fit with the classic reports of PE development following trauma but suggests an interesting hypothesis about the mechanism of formation of immediate PE: inflammation related to direct chest injury and autonomic dysfunction leading to vasospasm and thrombosis have been suggested as potential contributors to immediate PE pathophysiology following trauma, [18] a consequence of the amount of kinetic energy transmitted across the chest.

The association of high energy injury mechanisms with immediate PE begs the question about whether these PEs need to be treated in the same way as PEs presenting in the typical way following injury. If these are, in fact, *de novo* intrapulmonary thrombi which form due to direct injury to the chest, therapeutic anticoagulation may be unwarranted. This question clearly requires further prospective research.

A number of patients received TXA as part of the trauma protocol within our maturing MTN. The potential thromboembolic risk profile of TXA in trauma patients remains a subject of ongoing debate, with several studies reporting an increase in thromboembolic events [19, 20] while a signal for increased incidence of VTE has not been seen in large RCTs [21] and observational studies.[22] The patients who received TXA were younger, had more severe injuries, and longer admissions. We observed a higher rate of PE in patients treated with TXA but this was not statistically significant. We did not examine for the beneficial effects of TXA in this study. Clearly, drawing further conclusions is unwise given the differences between the groups.

When examined more broadly, therapeutic anticoagulation was used inconsistently in our cohort. In patients with immediate PE alive 72 hours after admission the time to full anticoagulation was delayed due to clinical reasons in 4/11 (36%) immediate PE patients.

Within this subgroup of delayed therapeutic anticoagulation immediate PE patients one VTE recurrence (at day 14) was recorded in a patient who had started tLMWH on day 13.

These findings arguably lend support to other studies [9-11] where immediate PEs detected on initial CT, and subsequently not anticoagulated, did not develop into clinically significant PEs. It is however troubling that one patient developed clinically significant PE following a diagnosis of immediate PE and whilst the evidence is strengthening that it is safe not to offer therapeutic anticoagulation to patients with immediate PE,[23, 24] further refinement is needed, perhaps involving risk stratification tools to better define which patients do indeed need to be considered for therapeutic anticoagulation.

It is also unclear whether SSPE require treatment. With the recent improvements in CT technology we asked whether increasing CT detector density would increase the number of SSPE diagnosed and subsequently increase the risk of over-treatment of PE in complex trauma patients. Previously, with the transition from single-slice to 64-slice multi-slice scanners in the last two decades, several studies showed that more SSPEs were being diagnosed with higher density, higher sensitivity CT scanners [17] raising the possibility that more SSPEs would be diagnosed with 128-slice scanners. However, in this study population there was no significant difference in the number of SSPEs diagnosed by 64 and 128-slice scanners allaying fears of over-diagnosis and over-treatment.

This retrospective study of routinely collected data has several limitations. A proportion of PEs were diagnosed using an arterial phase trauma protocol rather than a PE protocol and, given that PEs have been shown to be over-diagnosed in routine clinical practice with dedicated CT pulmonary angiogram studies,[25] it seems plausible that some patients could have had false positive CT results. The total number of immediate PEs, although the largest in any study to date, is still small making it difficult to draw firm conclusions about the clinical significance and management of immediate PE. Furthermore, there may be an under-reporting of late PE

owing to repatriation and discharge of patients from our centre. Finally, in PE patients, the timing of anticoagulation was influenced by concomitant injuries rather than a specific institutional protocol.

This study suggests a number of avenues for further research into the natural history of VTE following trauma, and its treatment. Given the low incidence of the sub-types of this disease much of this research will need to be prospectively conducted in a multi-centre model using national databases combined with local electronic patient record data. More specifically, the key outcome of these studies should be accurate selection of patients who require therapeutic anticoagulation following trauma, and the timing of its administration.

Conflict of interest

The authors have no conflicts of interest to report.

Funding

No funding was received for this work. DKM is supported by the Cambridge Biomedical Research Centre National Institute for Health Research (UK) and by a European Union FP7 Grant to the CENTER-TBI study. VFJN is supported by an Academy of Medical Sciences/The Health Foundation Clinician Scientist Fellowship.

Author Contribution Statement

TEG – literature search, data collection, data analysis, manuscript preparation.

JES – data collection, manuscript preparation.

AE – data analysis, manuscript preparation, critical revision.

VFJN - data collection, manuscript preparation.

AL – manuscript preparation, critical revision.

ADC – study design, critical revision.

DKM – study design, critical revision.

ROL – literature search, study design, data analysis, data interpretation, manuscript preparation, critical revision, project supervision.

REFERENCES

1) Geerts WH, Code KI, Jay RM, et al. A prospective study of venous thromboembolism after major trauma. *N Engl J Med* 1994;331:1601-1606.

2) Rogers FB. Venous thromboembolism in trauma patients. *Surg Clin North Am* 1995;75:279-291.

3) Shuster R, Mathew J, Olaussen A, et al. Variables associated with pulmonary thromboembolism in injured patients: a systematic review. *Injury* 2017;1:1-7

4) Owings JT, Kraut E, Battistella F, et al. Timing of the occurrence of pulmonary embolism in trauma patients. *Arch Surg* 1997;132:862–8677.

5) Kakkar VV, Howe CT, Flanc C, et al. Natural history of postoperative deep vein thrombosis. *Lancet* 1969;2:230–232.

6) King AD, Bell SD, Stuttle AWJ, et al. Platelet imaging of thromboembolism: natural history of postoperative deep venous thrombosis and pulmonary embolism illustrated using the ^{111}In-labelled platelet-specific monoclonal antibody, P256. *Chest* 1992;101:1597–1600.

7) Knudson MM, Ikossi DG, Khaw L, et al. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. *Ann Surg* 2004;240: 490–498.

8) Holley AB, Petteys S, Mitchell JD, et al. Thromboprophylaxis and VTE rates in soldiers wounded in Operation Enduring Freedom and Operation Iraqi Freedom. *Chest* 2013;144:966–973.

9) Velmahos GC, Spaniolas K, Tabbara M, et al. Pulmonary embolism and deep venous thrombosis in trauma: are they related? *Arch Surg* 2009;144:928–932.

10) Lewis CR, Davis MK, Danner OK, et al. Pulmonary embolism diagnosed immediately following blunt trauma. *International Journal of Case Reports and Images* 2013;4:248-251.

11) Lundy JB, Oh JS, Chung KK, et al. Frequency and relevance of acute peritraumatic pulmonary thrombus diagnosed by computed tomographic imaging in combat casualties. *J Trauma Acute Care Surg* 2013;75: S215–S220.

12) UK National Health Service Standard Trauma Contract for Major Trauma Service. https://www.england.nhs.uk/wp-content/uploads/2014/04/d15-major-trauma-0414.pdf. Published November 2013. Accessed October 10th 2017.

13) Thomeer MG, Pattynama PM, Hartmann IJ, et al. High incidence of isolated subsegmental pulmonary emboli on multi-slice spiral CT: a comparative clinical study. *Thromb Haemost* 2006;95:914–915.

14) The UK Trauma Audit and Research Network. https://www.tarn.ac.uk/. Updated March 25th, 2018. Accessed March 25th 2018.

15) Netto FS, Homer T, Ng J, et al. Pulmonary emboli after blunt trauma: Timing, clinical characteristics and natural history. *Injury* 2012;43(9):1502-6

16) Benns M, Reilly P, Kim P. Early pulmonary embolism after injury: a different clinical entity? *Injury* 2014;45:241-244.

17) Carrier M, Righini M, Wells PS, et al. pulmonary embolism diagnosed by computed tomography: incidence and clinical implications. A systematic review and meta-analysis of the management outcome studies. *J Thromb Haemost* 2010;8:1716-1722.

18) Knudson MM, Gomez D, Haas B, et al. Three thousand seven hundred thirty-eight post-traumatic pulmonary emboli: a new look at an old disease. *Ann Surg* 2011;254:625-632.

19) Cole E, Davenport R, Willett K, et al. Tranexamic acid use in severely injured civilian patients and the effects on outcomes. *Ann Surg* 2015;261: 390–394.

20) Valle EJ, Allen CJ, Van Haren RM, et al. Do all trauma patients benefit from tranexamic acid? *J Trauma Acute Care Surg* 2014;76:1373–1378.

21) Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010 376:23–32.

22) Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. *Arch Surg* 2012;147:113–119.

23) Yoo HH, Queluz TH, El Dib R. Anticoagulant treatment for subsegmental pulmonary embolism. *Cochrane Database Syst Rev* 2014; CD010222.

24) Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest* 2016;149:315-352

25) Hutchinson BD, Navin P, Marom EM, et al. Overdiagnosis of pulmonary embolism by pulmonary CT angiography. *AJR Am J Roentgenol* 2015;205:271-7.