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Original Article

Early post-traumatic pulmonary embolism in intensive care unit: incidence, risks factors, and impact outcome

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Abstract: Background: Venous thromboembolism (VTE) is a well-established complication of trauma. Recent studies suggest that pulmonary embolism (PE) may occur very early, and even immediately, after injury. The aim of this study is to analyze the incidence, risk factors and prognosis of early PE among ICU trauma patients. Patients and Methods: We conducted a twenty-month-long prospective cohort study, including all trauma patients with a confirmed PE diagnosis admitted to our ICU between January 1st, 2017 and August 31st, 2018. Early post traumatic PE was defined as pulmonary embolism diagnosed within the first 72 hrs of injury. All the patients who were included were systematically screened for early PE on day 3. Results: During the study period, 365 trauma patients were admitted. The diagnosis of post-traumatic PE was confirmed in 66 patients (18%). In our study, 27 patients (41.5%) developed a PE within 72 hrs of trauma. According to our analysis, the factors associated with the development of early post-traumatic PE in multivariate analysis were obesity (P=0.049; OR=4.04), high SOFA score (P=0.003; OR=1.67), and the use of surgical procedures (P=0.033; OR=4.87). Furthermore, sepsis and ventilator-acquired pneumonia were associated with late PE (P=0.019; OR=5.87). Overall, the mortality rate was at 19.7%. Yet, the patients who were diagnosed with early PE had a higher mortality rate compared to the late PE group (33% vs. 10.2%, respectively). We found that the only independent predictive factor of mortality among the patients with early post-traumatic PE included in this study was the APACHEII score on ICU admission (P=0.011; OR=1.44). Conclusion: Our study cohort showed that many of the post-traumatic PEs occur early in the post-traumatic period. To the best of our knowledge, this is the first prospective study conducted in an ICU to apply a systematic screening protocol for post-traumatic PE diagnosis. Further studies with larger patient populations are required to create more accurate predictive models.

Keywords: Post-traumatic pulmonary embolism, early pulmonary-embolism, intensive care unit, prognosis

Introduction

Venous thromboembolic complications, such as pulmonary embolism (PE), remain significant contributors to morbidity and mortality following traumatic injury, mainly in patients admitted to the intensive care unit (ICU) [1, 2]. PE has been reported as the third leading cause of death in patients that stay alive for the first twenty-four hours after a lesion [3, 4].

Indeed, trauma patients, in particular, carry a significantly increased risk for the development of venous thrombo-embolic (VTE) events. Despite the common use of VTE prophylaxis protocols, the incidence of VTE after an injury is still high [3, 4]. Interestingly, recent literature suggests that patients are at risk for hypercoagulability early after the traumatic injury [5]. In fact, Many PEs are being diagnosed within the first few days, and a significant number are being diagnosed as early as the first 24 hours after injury [6-11]. In recognition of early hypercoagulability and formation of PEs relatively soon after trauma, on the one hand, and the bleeding concerns that often lead to a significant delay in the start of chemical VTE prophylaxis, mainly among patients with traumatic brain injury, on the other hand, the timing to start prophylaxis regimens raises dilemma. Moreover, these findings [6-11] call into question whether we should consider an updated understanding of the pathophysiology of post-traumatic VTE.

However, a small number of studies have so far been published about early post-traumatic PE [6-9]. Also, except for the study conducted by Darabadi F [9], none of them concerned an ICU population and they were all conducted in level 1 trauma centers [9].

We hypothesize that "early" and "late" PEs may actually represent separate clinical entities with distinct underlying pathophysiology and different risk factors. To investigate this question, we set to determine if "early" and "late" PEs exhibit different independent risk factor profiles and independent outcomes. If specific patients at risk for early PE could be identified, more informed decisions regarding prophylaxis could be made [3, 12]. Therefore, the aim of the present study was to analyze the incidence of early post-traumatic PE among ICU trauma patients, identify patient characteristics and risk factors related to the early occurrence of PE and study its outcome on ICU patients.

Patients and methods

There is no conflict of interest related to the research described above. This study was approved by the institutional review board "COMITE DE PROTECTION DES PERSONNES SUD" and the requirement for written informed consent was waived by the ethics committee.

Study design and participants

We conducted a twenty-month-long prospective cohort study, including all trauma patients with a confirmed PE diagnosis who were admitted to our ICU between January 1st, 2017 and August 31st, 2018. Patients were included in the study if they were 16 years of age or older and diagnosed with a PE, as determined by Computed Tomography Pulmonary Angiography (CTPA) results. The exclusion criteria concerned patients with less than 16 years of age, those with acute kidney injury, patients who were too unstable, those who died and those who were discharged from the hospital within the first three days. All the patients were screened for PE on day 3.

PE diagnosis tools

PE diagnosis was confirmed based on CTPA results [13], showing one or more filling defects within the pulmonary vessels as a direct sign of PE. The diagnosis was, otherwise, confirmed based on echocardiographic findings including direct visualization of a thrombus in the pulmonary artery. In our institution, a systematic screening for PE was performed on day 3. Furthermore, radiological explorations were also performed whenever PE was clinically suspected (in case of unexplained hypoxemia and/or shock).

Data-base collection and follow-up

Our department is a 22-bed medical surgical ICU. It is a first-line medical center that cares for a population of over one million inhabitants in Tunisia, with about 1200 patients hospitalized annually. On ICU admission, all patients were scored according to the Glasgow coma scale (GCS). The SOFA, APACHEII and SAPSII scores [14-16], were also recorded on admission and on the day of PE diagnosis. The data recorded included patients' demographics, body mass index (BMI), detailed information on clinical and biological parameters and relevant therapeutic measures were registered on admission and during the ICU stay. The diagnosis of disseminated intravascular coagulation (DIC) [17], sepsis, and ventilator-associated pneumonia (VAP) [18] were also recorded on the day of PE diagnosis. The pulmonary embolism severity index (PESI) score [19] was calculated on the day of PE diagnosis to classify patients with confirmed PE according to their early outcome. In addition, a Body-Scan was performed for all patients with major trauma on hospital arrival. The abbreviated injury score (AIS) [20], the injury severity score (ISS) [21], trauma circumstances, and injury characteristics - such as the presence of traumatic brain injury (TBI), spinal cord injury (SCI), lower extremity fractures, chest injury, or pelvic fractures - were then recorded. Depending on the initial clinical evaluation, other radiological investigations were performed and repeated, if needed, including: plain X-rays, computed tomography (CT)-scans, magnetic resonance imaging (MRI) and trans-thoracic echocardiography (TTE). The type of chemical prophylaxis used, days until the start of chemical prophylaxis, operative interventions requiring general anesthesia, and the use of blood transfusion during the first 72 hrs were also recorded for all the patients. The delay to PE diagnosis was also recorded. Patients who were diagnosed with a PE within 72 hrs of admission were classified as having "early" PE and were compared with those who were diag-

nosed with PE on or later than ICU day 4 ("Late PE"). The given therapeutic agents, either anticoagulant therapy alone or with thrombolytic agents, were recorded. Finally, the evolution during ICU stay and patients' outcome were recorded including mortality rates, ICU length of stay (LOS), days with mechanical ventilation, nosocomial infections, Hemorrhagic incidents related to anticoagulant therapy, pulmonary infarction and recurrent PEs. Venous thromboembolism prophylaxis during the analyzed time-period followed specific clinical practice guidelines [22, 23]. In our ICU, Intermittent Pneumatic Compressions (IPCs) were not available, elastic compression stockings were used unless contraindicated by lower extremity injuries. Pharmacologic prophylaxis was considered standard therapy for all trauma patients. However, the timing of initiation of pharmacologic prophylaxis was at the discretion of the trauma team and depended highly on any bleeding risk and injury patterns. In fact, in our ICU, we initiate preventive anticoagulation (with low molecular weight heparin) within 24 hours after ICU admission if the initial injuries did not worsen on a control brain CT-scan (performed in 24 hours, and at variable intervals thereafter based on clinical manifestations). Trauma patients received pharmacologic prophylaxis in the form of enoxaparin at a standard dose (40 mg subcutaneously, once daily). Patients with diminished renal function (creatinine clearance < 30 cc/min) were given unfractioned heparin (UFH) at a dose of 3000 units subcutaneously every 12 hrs. LMWH dosage was adjusted for patients at the extremes of weight (< 50 kg or > 150 kg) and at the discretion of the trauma team. Duplex ultrasonography was used to screen for DVT among trauma patients with a confirmed PE. Prophylactic vena cava filter insertion was not used in our study.

Outcome

The main objectives of this study were to investigate the incidence of early PE, associated risk factors, and mortality rates. The secondary objectives included mortality risk factors, patients' LOS, and total ventilation days.

Statistical modeling

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22. A *p*-value less than 0.05 was considered statistically significant for analysis. Continuous variables were reported as means (± SD). Categorical variables were reported as proportions and percentages. Patients diagnosed with a PE within 72 hrs of admission were classified as having early PE and were compared with those who were diagnosed with PE later in their ICU stay. Then, comparing survivors to the non-survivors, we analyzed the risk factors related to mortality among patients sustaining an early PE.

For univariate analysis, we used the Pearson Chi-square or Fisher exact test as appropriate for categorical variables. The continuous variables were examined for normality of distribution using the Shapiro-Wilk test. Student t-test was used to compare for differences between the groups for normally distributed variables and Mann Whitney U test for non-normally distributed variables. Next, a multivariate logistic regression analysis was performed by using the backward stepwise approach to identify factors that were independently associated with the occurrence of early PE and determine the factors that were independently predictive of death among patients sustaining an early post-traumatic PE. Odds ratios were estimated from the b coefficients obtained, with respective 95% confidence intervals (CI = 95%).

Some variables such as age and severity scores, including Glasgow coma scale, SAPSII score, APACHEII score, and SOFA score, were used to predict the early occurrence of post-traumatic PE as well as bad outcome and were analyzed using Receiver Operating Characteristic (ROC) curves. The area under the ROC curve, which was estimated by the method of Hanley and McNeill [24], provides a measure of the predictive accuracy of the test.

Results

Descriptive characteristics of all included patients on ICU admission

From January 1st, 2017 to August 31st, 2018, a total of 474 trauma patients were admitted into our ICU, among whom 365 patients met eligibility criteria and 66 were diagnosed with post-traumatic PE (The incidence of post-traumatic PE was 18%) (**Figure 1**).

In this study, patients were male in 96% of the cases. The mean age was 40 ± 14 years with a median of 36.5 years (**Figure 2**) and 32 patients (48.5%) had a BMI above 30 kg/m^2.

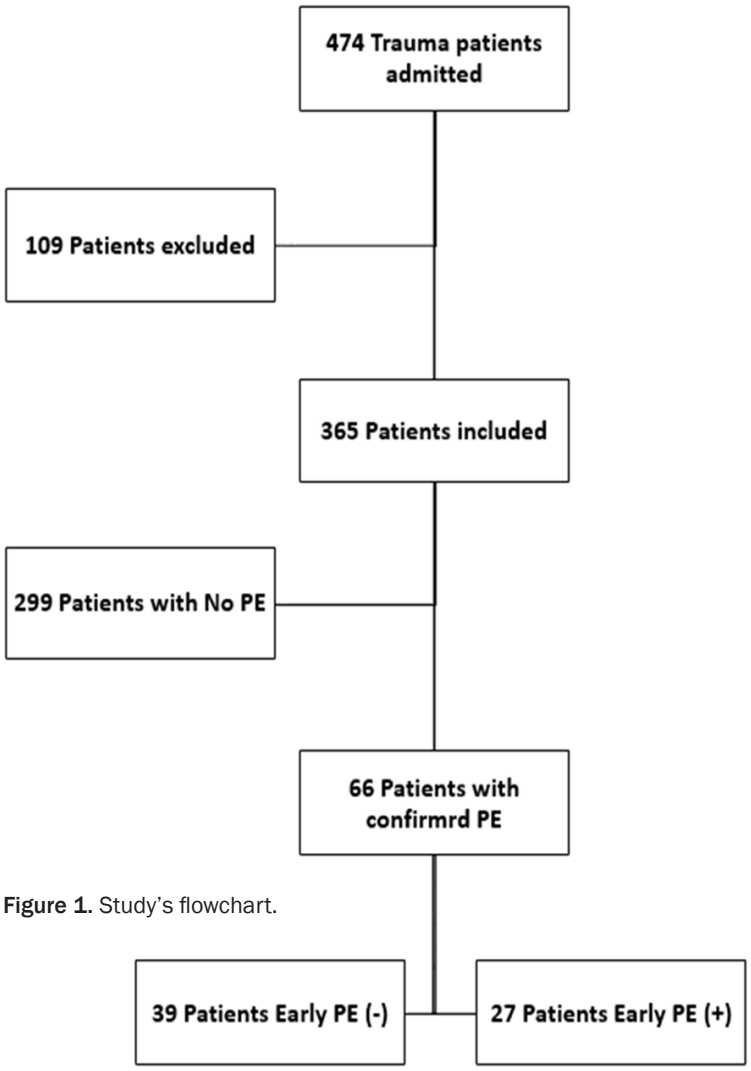

Figure 1. Study's flowchart.

Among the included patients, 53 patients (80%) had a TBI, 45 patients (68%) had a chest trauma and 12 (18%) had an abdominal trauma.

According to our investigation, 48 patients (72.7%) had a severe TBI with Abbreviated Injury Scale score for the head above three (AIS-head ≥3). Moreover, only 9 patients (13.6%) presented with long bone fractures in the lower extremities. The clinical presentation on admission of the study group (PE (+)) is shown in **Table 1**. Sixty-one patients (92.4%) required sedation and invasive mechanical ventilation on ICU admission. The mean GCS on ICU admission was at 8 ± 3. Thirty-eight patients (57%) were deeply comatose with a GCS less than 8. In our study, 16 patients (24.2%) showed signs of shock on ICU admission, requiring vasopressor support. Thirty-three patients (50%) underwent emergency surgical procedures requiring general anesthesia within the first 48 hrs. A total of 42 patients (48.5%) required blood transfusions within the first 2 days of admission. Transfusion with red blood cells units (RBCs) was required in 21 patients (33.3%), 27 patients (42.9%) needed fresh frozen plasma (FFP), while platelets transfusion was used in six patients (9%). **Table 1** summarizes all the characteristics of the entire population group on ICU admission.

Sixty-four patients (97%) received chemical prophylaxis for VTE. Mechanical methods using elastic compression stockings were applied in 42 cases (63.6%). The mean delay to starting chemical prophylaxis was 2.4 ± 1 days, with a median at 2 days and extreme values ranging from one to 14 days. At the time of PE diagnosis, sixteen patients (59%) were already receiving chemical prophylaxis (within 2 days after trauma). The mean delay to PE diagnosis was 6.7 ± 5.1 days with a median of 5 days. In addition, two patients were diagnosed with a PE on day 2 after injury. According to our analysis, 27 patients (41.5%) were diagnosed with PE within the first 72 hrs following trauma and the remaining 39 patients (58.5%) were diagnosed with a late PE (**Figure 3**).

Descriptive characteristics of all included patients on the day of PE diagnosis

On the day of PE_diagnosis, 62 patients (94%) were under mechanical ventilation. The mean P/F ratio was at 218 ± 88 (extreme values: 112 and 433) with a median at 217.5. Moreover, on the day of CTPA realization, 97% of the patients had a stable hemodynamic state. However, two patients developed shock requiring vasopressor support. Depending on the location of the thrombus, PE was interpreted as proximal in 61 patients (92%), distal in five (8%), and bilateral

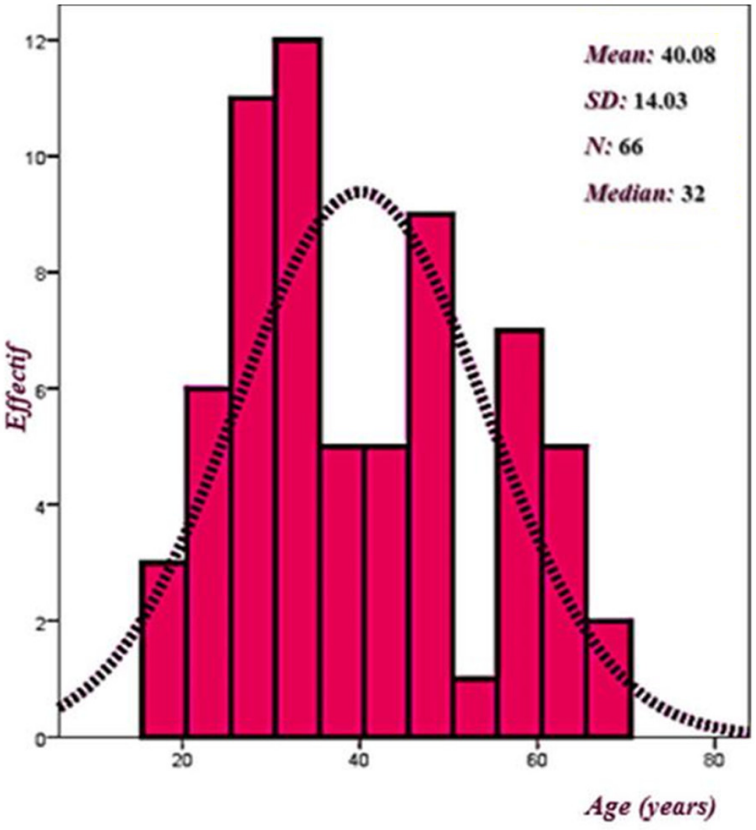

Figure 2. Distribution of patients according to their age.

in 15 (23%). Echocardiography was performed in 24 patients on the day of PE diagnosis showing an RV dilatation in 10 patients, isolated pulmonary arterial hypertension in 2 patients and a paradoxical-septal-motion in 2 patients. In eight patients with confirmed PE, the echocardiographic evaluation was normal. Of the 66 patients diagnosed with a PE, only 12 patients underwent evaluation for DVT, among whom seven (58%) had positive results. All the patients received curative-anticoagulant therapy. They were treated using continuous unfractionated heparin infusions in 58 patients (90% of the cases), with a median starting dose at 200 mg and with LMWH in eight cases. During the study period, we recorded no cases of bleeding attributed to the anticoagulant therapy.

Outcome

In this study, the mean length of ICU stay was at 22 ± 15 days, with extremes ranging from 4 to 72 days. The mean duration of mechanical ventilation was at 16 ± 11 days (with extremes ranging from 3 to 60 days). A total of 41 patients (63.1%) underwent elective tracheostomy for prolonged intubation, 42 patients (63.6%) developed a nosocomial infection during their ICU stay and 13 patients (19.7%) died. In our study, we found that compared to the late PE group, the early group was associated with high mortality rates (9/27 (33%) vs. 4/39 (10.2%); P=0.031 and OR= 4.25) (**Figure 4**).

Risk factors related to early occurrence of PE and its impact outcome

Univariate analysis revealed several factors associated with early PE occurrence after trauma (**Table 2**). In our study, we found that the early PE group was significantly older than the late PE group (P: 0.01). The proportion of obese patients (with a BMI over 30) was substantially higher in the early PE group (66% vs. 33%, with a *p* value =0.013). Moreover, patients with early PE had higher rates of long bone fractures of the lower extremities (6/27 (22%) vs. 2/39 (5%); P=0.048). In our study, patients that had developed PE early after trauma had a higher severity score with a mean SOFA score of 6.8 ± 2 vs. 5 ± 1.8 and P=0.001. **Table 2** provides an overview of basic characteristics and differences between the patients with and without early post-traumatic PE. Multivariate analysis showed that independent risk factors predictive of PE within 72 hours of trauma were high SOFA score, obesity, and the use of surgical procedures (**Table 3**).

Risk factors associated with death in the Early PE group

A number of variables were considered as possibly being associated with death. **Table 4** shows factors associated with death among the early PE group on univariate analysis. In contrast to the survivors, the non-survivors had older age (53 ± 15 vs. 41 ± 13 years, P=0.045) with high severity scores on ICU admission (**Table 4**). On the day of PE diagnosis, the non-

Table 1. The clinical presentation of the study group (PE (+)) on admission and on the day of PE diagnosis

Variables		*Number*	*Mean ± SD/ Proportion (%)*
Demographic characteristics	Age (years)	66	40 ± 14
	Obesity (BMI > 30)	66	32 (48.5%)
	Arterial hypertension	66	2 (3%)
	Chronic obstructive pulmonary disease	66	1 (1.5%)
	Epilepsy		1 (1.5%)
Injury assessment	Severe brain injury (AIS≥3)	66	48 (72.7%)
	Severe chest trauma (AIS≥3)	66	12 (18.2%)
	Severe abdominal trauma (AIS≥3)	66	2 (3%)
	Long bone fractures in lower extremities	66	9 (13.6%)
	Cerebral venous sinus thrombosis	66	5 (7.5%)
Severity scores	SAPSII score	66	31.4 ± 10
	APACHEII score	66	11.2 ± 4
	Sofa score	66	5.7 ± 2
	ISS score	66	34 ± 10
Clinical findings on admission	Circulatory shock	66	16 (24%)
	Shock index	66	0.76 ± 0.27
	Mechanical ventilation	66	61 (92%)
	P/F ratio	66	264 ± 88
Initial treatment	Sedation	66	61 (92%)
	Vasopressor support	66	16 (24%)
	VTE prophylaxis	66	64 (97%)
	Delay to VTE prophylaxis	66	2.5 ± 1.9
	Operative interventions within 48 hrs	66	33 (50%)
	Blood transfusions within 48 hrs	66	42 (48.5%)
	Tranexamic acid administration	66	13 (19.6%)
Clinical findings on the day of PE diagnosis	Temperature	66	37.7 ± 0.9
	SOFA score	66	6 ± 2
	P/F ratio	66	218 ± 88
	Hypoxemia (P/F ratio < 300)	66	59 (89%)
	Circulatory shock	66	2 (3%)
	Sinus tachycardia	66	43 (65%)
	Sinus bradycardia	66	10 (15%)
CTPA findings	Proximal PE	66	61 (92%)
	Distal PE	66	5 (8%)
	Bilateral PE	66	15 (13%)

AIS: Abbreviated Injury Scale; APACHEII: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; GCS: Glasgow Coma Scale; P/F ratio: the ratio of arterial oxygen partial pressure to fractional inspired oxygen; PE: Pulmonary Embolus; SAPSII: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Blood Pressure; HR: Heart Rate.

survivors had a higher SOFA score (7.5 ± 2 vs. 6.5 ± 2, *p* value =0.001). The ROC curve analysis showed that the best cut-off to predict mortality was 8.5 points (sensitivity =87.5%; specificity =83.3% and AUC ROC =0.90) (**Figure 5**).

There was no significant difference in the number of days on ventilator between the two groups (16 ± 12 vs. 15 ± 12, *p* value =0.72), nor in the length of ICU stay (21 ± 14 vs. 24 ± 15, P=0.39).

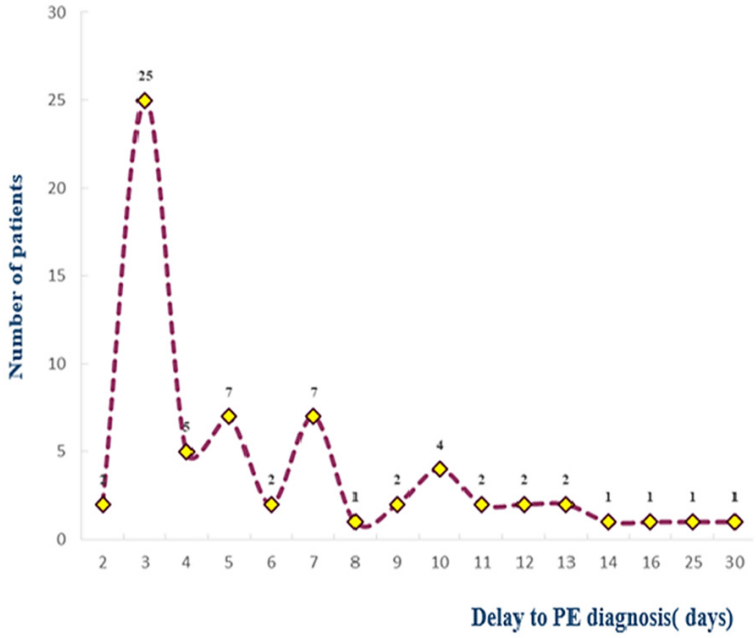

Figure 3. Delay to PE development.

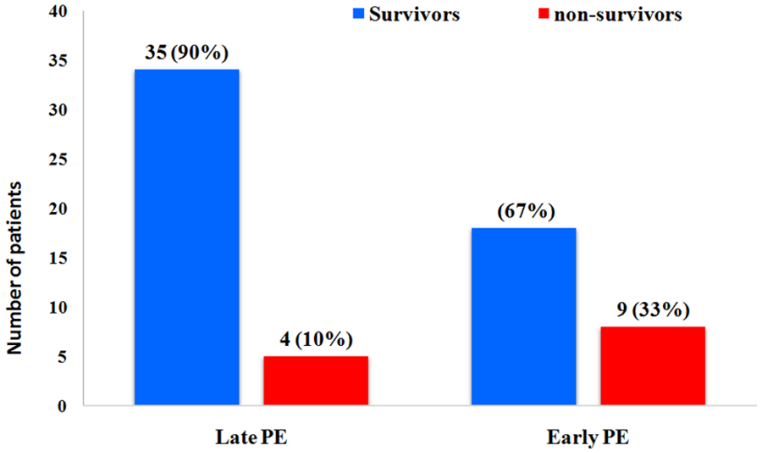

Figure 4. Mortality rates in the early group vs. the late group.

Discussion

Our study confirms that early Post-traumatic PE is frequent and associated with poor outcome compared to late PE. It is well-demonstrated, nowadays, that traumatic injuries carry a considerably increased risk of VTE events [25-29]. Our study confirms that post-traumatic PE is a frequent complication of trauma with an overall incidence of 18%. Data about the incidence of PE among trauma patients vary widely, ranging from 0.35% to 24% [1, 27, 28, 30]. In fact, differences in population characteristics, severity of injury, and screening protocols may account for much of the variability in the reported incidences. To the best of our knowledge, systematic screening has never been performed. In the current study, we reveal a more than 2 to 6-fold increase in PE incidence over the past decade [28, 31]. In fact, in a previous prospective study conducted in our ICU [28], the incidence of post-traumatic PE was only 3.2%. This apparent increase in post-traumatic PE incidence in comparison with published studies [31] can be explained by multiple factors including the severity of the studied population with 98% suffering from major trauma, the delay and posology of chemical prophylaxis used, and advances in CT scanning technologies. However, we could argue that the increase in PE rates could be related to a great extent to the use of a systematic screening protocol, even in patients who are clinically asymptomatic. Until recently, screening for asymptomatic pulmonary embolism was impractical. Similarly, in a study by Schultz [30, 32], the incidence of occult PE was much higher than commonly reported. They documented a 24% incidence of asymptomatic PE in 90 moderately to severely injured trauma patients undergoing surveillance using systematic contrast-enhanced helical CT scanning [30, 32].

Traditionally, it has been thought that PEs occur most commonly between day 5 and day 7 following the traumatic event and that they are rare earlier than day 4 [33]. This concept resulted mainly from classical teaching endorsing the belief that post-traumatic PE originates from deep venous thrombosis of the lower extremities and the pelvis. And because stasis, as a part of the classic Virchow triad, has been considered the predominant factor in the for-

Table 2. Differences between the patients with and without early post-traumatic PE on univariate analysis

Variables		*Number*	*Mean ± SD/Proportion (%)*		*P* value
			Early PE	Late PE	
Demographic characteristics	Age	66	45.3 ± 15	36.4 ± 12	0.01
	Obesity (BMI > 30)	66	44 (66%)	22 (33%)	0.013
Severity scores	GCS on admission	59	8.3 ± 3	8.8 ± 4	0.65
	SAPSII score on admission	66	34.4 ± 9	29.4 ± 10	0.51
	APACHEII score on admission	66	12.4 ± 4	10.3 ± 3	0.056
	SOFA score on admission	66	6.8 ± 2	5 ± 1.8	0.001
Injury assessment	Injury Severity Score	66	35.3 ± 9	34.2 ± 11	0.66
	Lower extremity long-bone fractures	8	6 (22%)	2 (5%)	0.048
	AIS_Head	59	3.5 ± 2	3.7 ± 1	0.8
	AIS_Face	49	1.8 ± 1	2.1 ± 1	0.45
	AIS_Spine	10	0.41 ± 1	0.39 ± 1	0.96
	AIS_Chest	45	2.15 ± 1	2.2 ± 1	0.86
	AIS_Abdomen	12	0.7 ± 0.5	0.4 ± 0.2	0.41
	AIS_Extremities	25	1.4 ± 1	0.7 ± 0.5	0.09
Hemostasis	DIC	6	5 (22%)	1 (2%)	0.041
Clinical findings (on the day of PE diagnosis)	P/F ratio	66	190 ± 57	238 ± 72	0.006
Initial treatment	Transfusions rate	40	20 (74%)	20 (51%)	0.001
	RBC transfusions	21	14 (51.8%)	7 (17.9%)	0.007
	FFP transfusions	27	18 (66.6%)	9 (23.7%)	0.001
	Surgical procedures	33	18 (66.6%)	15 (38.4%)	0.044

AIS: Abbreviated Injury Scale; APACHEII: Acute Physiology and Chronic Health Evaluation II; BMI: Body Mass Index; DIC: Disseminated Intravascular Coagulation; FFP: Fresh Frozen Plasma; GCS: Glasgow Coma Scale; P/F ratio: the ratio of arterial oxygen partial pressure to fractional inspired oxygen; RBC: Red Blood Cell; SAPSII: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment.

Table 3. Independent variables predictive of early PE

Variables	*P value*	*Odds Ratios*	*95% CI*
SOFA score	0.003	1.674	1.19-2.36
Obesity	0.049	4.04	1.00-16.40
surgical measures	0.033	4.87	1.13-20.83

SOFA: Sequential Organ Failure Assessment.

Table 4. Factors associated to death among the early PE group

Variables	*Outcome*	*Mean*	*± SD*	*P value*
Age	Survivors	41	13	0.045
	Non-survivors	53	15	
GCS on admission	Survivors	9	3	0.042
	Non-survivors	6.5	2	
SAPSII score on admission	Survivors	30	7	0.004
	Non-survivors	41	10	
APACHEII score on admission	Survivors	10	3	0.001
	Non-survivors	16	4	
SOFA score on admission	Survivors	6.5	2	0.001
	Non-survivors	7.5	2	
AIS score of the spine	Survivors	0.1	0.01	0.049
	Non-survivors	1	0.7	

AIS: Abbreviated Injury Scale; APACHEII: Acute Physiology and Chronic Health Evaluation II; GCS: Glasgow Coma Scale; SAPSII: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment.

mation of DVT in trauma patients, it has been thought that these events occur most commonly after 5 or even 7 days following injury [6-8, 33, 34]. However, reviewing the literature, we noticed an increasing trend in the number of PEs diagnosed during the very early phase following injury. Our findings were consistent with recent data, suggesting that a significant proportion of post-traumatic PEs actually occurs very early and even immediately after injury [6-9, 33, 35]. This significant decrease in the delay to PE diagnosis might be due to a lower threshold for PE clinical suspicion. In addition, "Late" PE may, nonetheless, be a delay to the diagnosis of a previously, earlier installed pulmonary clot.

Traditionally, it was commonly believed that post-traumatic PE originates from deep venous thrombosis of the lower extremities and

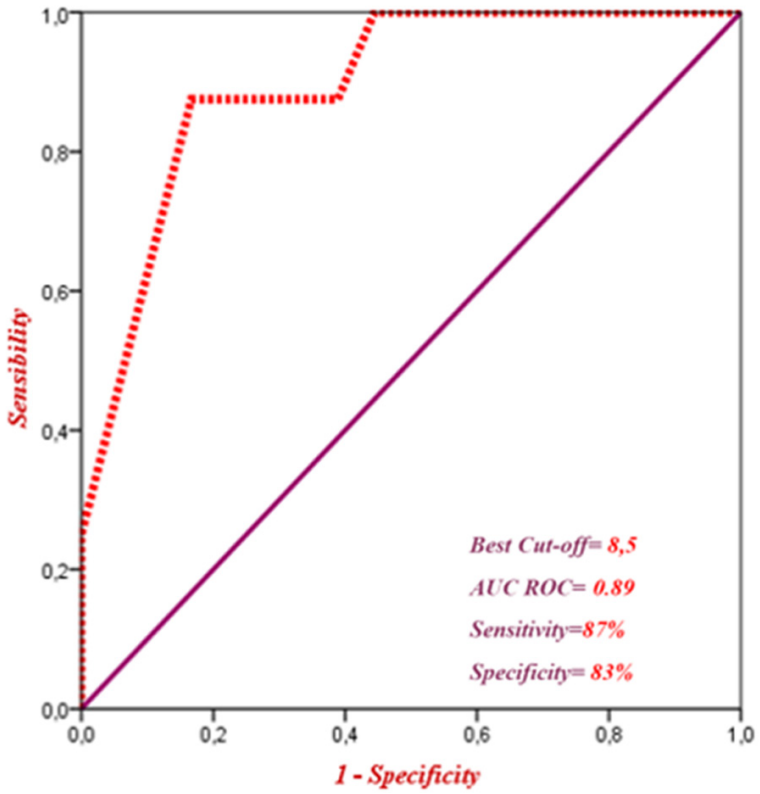

Figure 5. ROC Curve of SOFA score on the day of PE diagnosis.

pelvis [33]. However, PE and DVT do not always coexist, and there is actually little evidence that PE originates from DVT of peripheral veins. This last hypothesis was insufficiently discussed in the literature [36]. Several recent studies show that an increased proportion of post-traumatic PEs are being diagnosed very early, and even immediately, after injury [6-11]. Based on these reports and on our own study, we postulate that PEs diagnosed "early" after trauma may be related to a different underlying pathophysiology. However, demonstrating this would be extremely challenging. Two main explanations for early pulmonary embolism in trauma exist. The first possibility is the presence of an undiagnosed thrombophilia, congenital or acquired after trauma [37]. The second possibility was advanced by Velmahos [36] who showed that the majority of patients sustaining early post-traumatic PE were not diagnosed with DVT, based on computed tomographic venography of the pelvis and the lower extremity veins, suggesting that pulmonary clots may occur "de novo" within the lungs. This hypothesis was supported by other studies [38, 39], suggesting local inflammation as a possible etiology for "in situ" formation of pulmonary thrombosis [39]. A third hypothesis was advocated by Brakenridge [7] who suggested the existence of an unknown underlying molecular mechanism associated to fractures contributing to the early occurrence of PE. In fact, reviewing the literature, lower limb fractures were found to be the most frequent factor associated with early PE [6-9]. Moreover, obesity and age are both determined to be predictors for early PE development [6-9]. Furthermore, the heterogeneity among studies limits reliable conclusions regarding the true risk factors for the timing of the occurrence of post-traumatic PE. According to our analysis, the factors associated with the development of early post-traumatic PE were: older age, obesity, high SOFA score, hypoxemia, DIC, the need of blood transfusions and surgical procedures, and long bone fracture. The ISS and some injury patterns including TBI, severe chest trauma, and spinal cord injury were not statistically associated to the timing of occurrence of post-traumatic PE. These findings could be related to the fact that in our study population, 98.5% presented with major trauma and 73% were diagnosed with severe TBI on admission, contrasting with the heterogeneity in injury severity of the other studies [6-8], presumably because they were conducted in trauma centers and did not focus on severely injured ICU population. In our study, only obesity, high SOFA score, and the use of surgical procedures were independently associated with early PE occurrence. In fact, fat mass is responsible for chronic inflammation, leading to increased VTE risk and a reduced fibrinolysis [40]. As for surgery, even though it is known to be a risk factor for thrombo-embolic events, the commencement of the process leading to PE formation actually has no clear outset [33]. The use of radioactive-labeled fibrinogen years ago [41] demonstrated that patients undergoing surgery for major injury had evidence of clotting in leg veins and that, inter-

estingly, all of the patients who subsequently developed clinical complications had increased radioactivity in their leg veins during surgery. So, one might conclude that the clotting starts on the operating table and proceeds from there.

In our study, patients diagnosed with early PE had higher mortality rates compared to the late PE group. However, the proportion of deaths in which PE was the actual cause, was not determined in this study and not all deaths related to major trauma could be attributed to PE. In fact, the high mortality rate in our study could be largely explained by the severity of the patients. Therefore, we presume that outcome was probably related, substantially, to patients' characteristics and underlying diseases. Accordingly, the severity of the population on admission, stated by a high APACHEII, was an independent predictive risk factor of mortality among patients sustaining early PE. We believe these patients should benefit considerably from an early initiation of LMWH or the placement of IVC filters in case of contra-indications.

Although this study's findings raise several areas for future investigation, it does have some limitations. In fact, this research was based on a single-center data set. Besides, ultrasonography of the lower extremity veins and echocardiographic assessment were performed in a minority of patients. Moreover, none of the included patients underwent work-up for specific hemostatic disorders and there were no data collected regarding the postmortem exam. Therefore, the proportion of deaths in which PE was the actual cause was not determined in this study.

With regards to the above-mentioned limitations, we should recognize that this study was the first prospective cohort analyzing early post-traumatic PE in an ICU population and applying a systematic uniform screening protocol based on CTPA realization on day 3.

Conclusion

Our findings showed that in a population of patients with severe trauma, pulmonary embolism is a frequent and life-threatening complication. The early occurrence of PE along with the lack of association between PE and DVT could be related to an "in situ" formation of a clot in the peripheral pulmonary arteries caused by direct inflammation of pulmonary vessels after injury. This assertion requires further investigations. Our results cannot conclusively prove this hypothesis, but they lend support to this argument. This knowledge should lead clinicians to maintain a high index of suspicion in injured patients, regardless of the length of hospitalization. Finally, we recommend that future studies should evaluate the prophylactic protocols to be used and revise the dosage of unfractionated heparin to be administered in the specific context of post-traumatic patients.

Disclosure of conflict of interest

None.

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