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Pulmonary embolism in intensive care units: More frequent or more Known? Prospective study of 75 cases

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Abstract

Purpose: to evaluate the current rate of pulmonary embolism (PE) in our medico-surgical intensive care unit (ICU), to identify risk factors, and to determine the outcome of PE in ICU.

Methods: We performed a prospective cohort study of consecutive patients requiring intensive care admission during a one-year period. We included, in this prospective study, all the patients with confirmed PE admitted in ICU with more than 18 years of age, and expected to stay in ICU for more than 48 hours. Only the patients who had a clinical suspicion (unexplained hypoxemia and/or shock) for PE underwent diagnostic studies.

Results: During the study period, 842 patients were admitted in our ICU. One hundred and two patients were excluded. The diagnosis of PE was confirmed in 75 patients (10.1%). In our study, all patients (100%) had received some forms of pharmaceutical prophylaxis (PP) during ICU stay. The median time from ICU admission to diagnosis of PE was 6 days. The diagnosis of PE was made by spiral CT in 74 patients (98.7%), and by echocardiography in 1 case (1.3%). The mean ICU stay was 26.3 ± 26.5 days (median: 20 days). During their ICU stay, 73 patients (97.3%) developed one, or more, organ failure. Respiratory failure was the most observed (97.3%). Moreover, 38 patients (50.6%) developed nosocomial infections and 29 (38.6%) died. The multivariate analysis showed that the risk factors associated with mortality were the presence of shock the day of PE diagnosis and the presence of right ventricular dilatation on echocardiography.

Conclusion: Our findings confirm that subjects in the ICU are at high risk of PE, due to a high number of risk-factors. PE was associated with higher ICU mortality and a significantly higher ICU LOS. Our results invite to revise the preventive strategies of deep venous thrombosis and PE in patients requiring ICU admission.

KEYWORDS

intensive care unit, outcome, pulmonary embolism, shock index

1 | INTRODUCTION

Venous thromboembolism (VTE), which includes pulmonary embolism (PE) and deep venous thrombosis (DVT), remains a major challenge and represents severe complications in the care of critically ill patients.[1-5] Indeed, intensive care unit (ICU) patients are at a high risk of VTE because they are subject to several general risk factors for VTE (such as immobilization, age, obesity, past history of neoplasm, sepsis, recent surgery, trauma) and ICU-related risk factors (such as sedation, central venous catheterization, respiratory or heart failure and the use of vasoactive drugs).[1-5] In fact, in the ICU, most patients are severely ill requiring sedation and mechanical ventilation (MV).[4,5] However, despite recent advances in prophylactic, diagnostic and therapeutic modalities, PE remains one of the important causes of in-hospital morbidity and mortality.[1-5] In fact, PE is one of the three main illnesses frequently identified during autopsies, but clinically under-diagnosed.[6,7] Indeed, autopsy studies report a high incidence of PE (27%) in critically ill patients; of these, only one-third were clinically suspected.[6,7] In fact, in ICU, PE is a difficult diagnosis, which may be missed because of a nonspecific clinical presentation, principally in patients requiring MV. As a consequence, the prevalence of PE, although well-documented in the general population, remains unclear in ICU because systematic screening is not methodically performed.[1-5] Up to this day, little is known about the incidence and prevalence of PE in ICU, with a reported rate ranging from 0.5% to 18.7%.[2-5] However, the analysis of recent literature,[2,3,5] showed a higher incidence of PE in comparison with the data published in the last decade.[3,8,9] Moreover, it was well-established that the development of PE was associated with a high mortality rate (7% to 27%), a high rate of nosocomial infections and a prolonged ICU and in-hospital length of stay (LOS).[1-5] Eight years ago, we reported a low rate (1.9%) of PE in our ICU.[4] Moreover, we are attentive of the small number of published studies investigating the incidence and prevalence of PE in ICUs.[1-5]

Based on these insufficient published data and the improvement of detection methods, we have concluded that further researches need to be conducted about the incidence, risk factors and outcome of PE in ICUs. Consequently, we have carried out this prospective study. The primary objective was to evaluate the current rate of PE in our medico-surgical ICU. The secondary objectives were to identify the risk factors, and to determine the outcome of PE in our ICU.

2 | MATERIALS AND METHODS

This study was approved by an internal review board. The need for informed consent was waived because of the study design.

This prospective observational study was conducted over a one-year period, in a 22-bed medical–surgical-ICU in a university hospital, between June 2015 and May of 2016. We included, in this prospective study, all the patients with confirmed PE admitted in ICU with more than 18 years of age, and expected to stay in ICU for more than 48 hours. Were excluded all the patients with acute renal failure.

In our institution, the diagnosis of PE is usually suspected by the presence of tachypnea, dyspnea, pleuritic chest pain and hemoptysis. However, in our ICU, most of the patients required sedation and MV, and the diagnosis of PE was usually suspected when unexplained hypoxemia and/or shock, and arterial hypotension occurred. The diagnosis of PE was made via spiral helical computed tomography (CT) scan showing one or more filling defects or obstruction in the pulmonary artery or its branches.[10] The diagnosis could also be confirmed when echocardiography showed a direct visualization of a thrombus in the pulmonary artery. All patients were examined clinically and radiological explorations were performed (spiral helical CT scan, and echocardiography) if PE and/or VTE was clinically suspected. Doppler for lower limb DVT, was not systematically performed, because it was not available in our ICU. As a consequence, for a doppler of a lower limb DVT to be done, the patient had to be transferred to the radiological department. Only those patients who had a clinical suspicion for PE underwent such diagnostic studies.

For each patient, we recorded age, sex, body mass index (BMI), cause for ICU admission, medico-surgical status, personal history of DVT/VTE and known thrombophilia disorder. Moreover, risk factors (immobility, recent surgery, congestive heart failure, chronic obstructive pulmonary disease (COPD), cancer etc.) were also collected.

The use and the delay of preventive anticoagulant agents, the timing of development of PE and the clinical manifestations associated with the PE were also recorded for each patient.

Other independently recorded factors were vasoactive drugs use, central venous catheter use and site of implantation and the presence of sepsis.

Moreover, for each patient, the severity of illness was estimated with simplified acute physiology score (SAPS II),[11] SAPSIII score[12] and according to the SOFA score.[13] The shock index[14] was also calculated the day of ICU admission and the day of PE diagnosis. The systemic inflammatory response syndrome (SIRS)[15] was also researched on admission and during ICU stay.

In our study, the presence of arterial hypoxemia is defined by arterial oxygen saturation in room air $\leq$92%. In patients receiving MV, arterial hypoxemia is defined as a PaO2/FiO2 ratio <300. For each patient, we have analyzed the location of the most proximal thrombus in the central, lobar, segmental, or subsegmental pulmonary artery.

High-risk PE is defined as the presence of shock or persistent hypotension. Whereas sub-massive PE is defined as stable hemodynamics associated with the presence of echocardiographic right ventricular (RV) dysfunction based on RV dilatation (end diastolic diameter >30 mm) or hypokinesia or abnormal movement of the interventricular septum with or without tricuspid regurgitation.[16] Therapeutic agents given, either unfractionated heparin alone or thrombolytic agent, were noted. During the ICU stay, all complications were recorded: nosocomial infections,[14] pneumonia, thrombocytopenia, gastrointestinal bleeding, cerebral hemorrhage and hematomas. For each patient, the number of organ failure[15] was calculated on admission and on the day of diagnosis of PE, ICU and hospital mortality rate and length of stay (LOS) were also recorded.

The estimation of the rate of confirmed PE among consecutive ICU patients during the study period represents the primary objective of this study. The secondary objectives were to identify risk factors, and to determine the outcome of PE in our ICU.

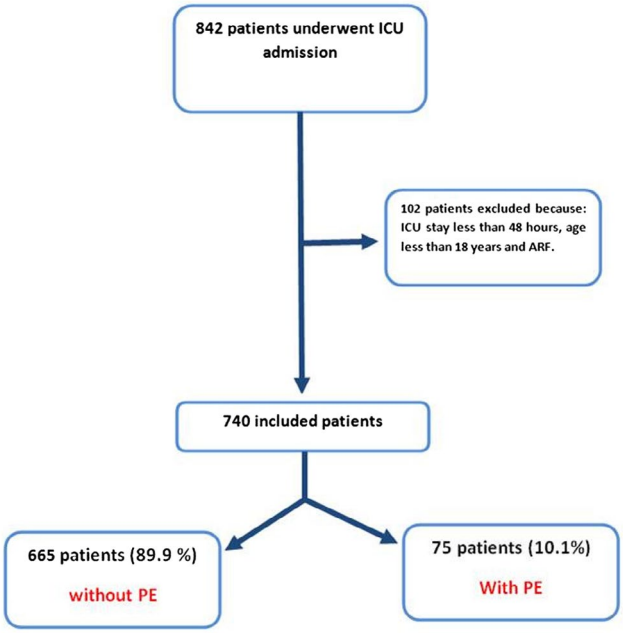

FIGURE 1 The study flow chart (PE: pulmonary embolism; ARF: acute renal failure)

2.1 | Statistical analysis

We considered the rate of PE as the number of patients with confirmed PE divided by all patients admitted to our ICU during their stay in the ICU. Categorical data are expressed in proportion and subgroups (survival and death) and were analyzed by the Chi-square test. Continuous variables are expressed as means (± SD), median and interquartile range (IQR), and subgroups evaluated by Student t test. Risk factors were evaluated in univariate analysis and in multivariate analysis by a multiple logistic stepwise regression procedure. The independent effect of each variable on mortality was assessed with the multivariate logistic regression analysis backward conditional method. To build the model, a purposeful selection method was used to select a subset of covariates that were considered to be clinically important, adjusting for confounders and statistical significance. Odds ratios are estimated from the beta coefficients obtained, with respective 95% confidence intervals (CI 95%). Final P values <0.05 were considered significant.

3 | RESULTS

During the study period, 842 patients were admitted in our ICU. One hundred and two patients were excluded because of an age less than 18 years, an ICU length of stay less than 48 hours, and/or acute renal failure (ARF). The diagnosis of PE was confirmed in 75 patients (10.1%), who were all included in this study (Figure 1). In 42 patients, the diagnosis of PE was clinically suspected, but not confirmed by spiral helical CT-Scan.

In our study, the most frequently identified causes of ICU admission were: polytrauma in 40 patients (53%), respiratory distress in 14 (18.6%), shock in 12 (16%), coma in 4 (5.3%) and post-surgical admissions in 5 (6.6%). There were 63 (84%) males and 12 (16%) females. The mean age (± SD) was 53 ± 18 years (median: 53). Mean SAPS II on ICU admission was 37.2 ± 11.6 (median: 32). Mean SOFA Score on ICU admission was 5 ± 1.7 (median: 5). Moreover, 38 patients (50.6%) had an obesity with BMI > 30kg/m^2, and 12 patients (16%) had a Disseminated intravascular coagulation (DIC) on ICU admission. Table 1 reports the patients' characteristics on ICU admission.

Thirty-eight patients (50.7%) had one or more comorbid conditions. The most common past medical diseases were arterial hypertension in 21 (28%) patients, exacerbation of chronic obstructive pulmonary disease in 8 (10.7%) patients, chronic heart failure in 9 (12%) patients and diabetes mellitus in 5 (6.7%) patients. However, none of the patients had a personal history of DVT/VTE or known thrombophilia disorder (Table 2). Additionally, all patients included in this study have one or more risk factors of PE (Table 2).

In our study, all patients (100%) had received some forms of pharmaceutical prophylaxis (PP) with equivalent of 40 mg of enoxaparine, during ICU stay. Moreover, in 23 patients (30.7%), mechanical prophylaxis was associated for the prevention of DVT.

The mean delay of PE development was 7.2 days (range 1-30 days). The median time from ICU admission to diagnosis of PE was 6 days. As illustrated in Figure 2, almost 46.6% of all patients developed PE within the first 5 days of ICU

TABLE 1 Patients characteristics on ICU admission

Parameters	Results [median]	Percentage
Age (years)	53 ± 18 [53]	
Sex M/F	63/12	
SAPS II	37.2 ± 11.6 [32]	
SAPS III	43.4 ± 12.4 [43]	
Shock index	0.85 ± 0.26 [0.85]	0.85
SOFA score	5 ± 1.7 [5]	
BMI > 30 kg/m^2	38	50.6
Class "A" in the APACHE system	38	50.6
Medical patients	30	40
Surgical patients	5	6.7
Poly-trauma-patients	40	53.3
HR (beats/min)	101 ± 16	
SBP (mm Hg)	123 ± 21	
Shock	21	28
Use of catecholamine	20	26
Use of mechanical ventilation	68	90.6
Hypoxemia (PaO2/FiO2 < 300)	51	73.3
Body temperature (°C)	37.2 ± 0.9	
Glasgow Coma Scale score	11 ± 4[12]	
Infection (sepsis)	51	68
Use of antibiotics (yes/No)	41	54.7
Disseminated intravascular coagulation (DIC)	12	16
Multi organ failure	61	81

TABLE 2 Risk factors in all study groups

Parameters	Number of patients	%
Infection (Yes)	51	68
Age > 60 (years)	29	38.6
Immobility *(Bed rest)*	75	100
Obesity	26	34.7
Chronic cardiovascular disease	9	12
Use of mechanical ventilation	68	90.6
General anesthesia in first 24 h	68	90.6
Chronic Respiratory disease (COPD)	8	10.7
Diabetes	5	6.7
Stroke	7	9.2
Traumatic Brain injury	33	44
Chest Trauma	30	40
Pelvic fracture/abdomen injury	13	17.3
Fracture of Long Bones	17	22.7
History of genetic thrombophilia	0	0
History of DVT/VTE	0	0
Blood transfusion	23	30.7
Multi organ failure	73	97.3

hospitalization. The diagnosis of PE was made by spiral CT in 74 patients (98.7%), and by echocardiography in 1 case (1.3%). According to the thrombus location, PE was interpreted as proximal in 58 patients (77%), distal in 16 (21.3%) and bilateral in 7 (9.3%). In our study, ultrasonography of the legs was performed in only 35 patients (46.6%). The diagnosis of DVT was confirmed in only 8 patients (23%). Moreover, Echocardiography was performed in only 70 patients (93%), showing a RV dilatation in 34 (48.5%), RV free wall hypokinesis in 8 (11.4%) and a Paradoxical septal motion in 3 (4%). In one patient, echocardiography revealed a direct visualization of thrombus in the pulmonary artery.

Table 3 summarizes patients' characteristics on the day of PE diagnosis. On thecontrary, the comparison between Shock index (SI) the day of ICU admission and the day of PE development showed a significant increase in SI the day of PE development (0.85 ± 0.26 vs. 0.95 ± 0.26; $P = .027$) (Figure 3). Moreover, we have found a significant correlation between the Shock index and the PaO2/FiO2 ratio the day of PE development ($P = .02$, $R = -.25$) (Figure 4).

In our study, 69 patients (92 %) received curative anticoagulation. Intravenous unfractionated heparin was used in 64 patients (85.3%) and low molecular weight heparins were used in 5 cases (6.7%). Moreover, an inferior vena cava filter was implanted in two patients because the anticoagulant therapy was contraindicated. Under anticoagulant therapy, 7 patients (9.3%) developed a bleeding complication. Moreover, 4 patients (5.3%) developed Heparin-induced thrombocytopenia.

The mean ICU stay was 26.3 ± 26.5 days (median: 20 days, IQR: 8 to 35). During their ICU stay, 73 patients (97.3%) developed one or more organ failure. Respiratory failure was the most observed (97.3%). Moreover, 38 patients (50.6%) developed nosocomial infections. During their ICU stay, 29 (38.6 %) died.

Compared with survivors, patients who died were not found significantly older ($P = .15$). However, SAPSII (33.7 ± 11 vs. 42.7 ± 10.3; $P = .001$) and SAPSIII (39.8.7 ± 12 vs. 49.1 ± 11; $P = .001$) scores were significantly higher in the patients who died. Other factors associated with poor prognosis were: Shock (5/46 (10.8%) vs. 18/29 (62%); $P < .001$), RV dilatation on echocardiography (30% vs. 76%; $P = .001$) and elevated shock index on the day of PE development (0.88 ± 0.16 vs. 1 ± 0.35 $P = .004$). Table 4 summarizes all the factors associated with death in univariate analysis.

The multivariate analysis showed that the factors associated with a poor prognosis were the presence of Shock the day of PE diagnosis ($P = .009$; OR: 94; 95% CI = 3.08-287) and the presence of RV dilatation on echocardiography ($P = .026$; OR = 42.3; 95% CI = 1.56-114).

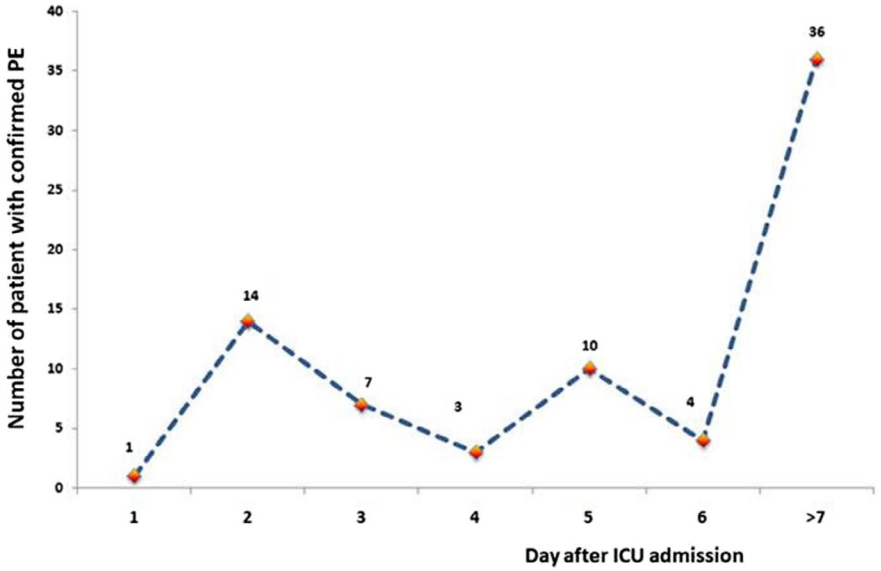

FIGURE 2 Delay of PE development in the studied group. As illustrated, 35 patients (46.6%) developed PE within the first 5 days of ICU hospitalization

TABLE 3 Patient-characteristics the day of PE diagnosis

Parameters	Results	% [median]
Tachycardia (>90 beats/min)	60	80
Shock	23	30.6
Use of catecholamine	23	30.6
SHOCK Index	0.95 ± 0.26	[0.89]
Use of mechanical ventilation	67	89.3
Hypoxemia (PaO2/FiO2 < 300)	73	97.3
PaO2/FiO2 ratio	182 ± 50	[180]
Serum lactate (mmol/L)	2.08 ± 0.52	[2]
Troponine (ng/mL)	0.49 ± 1.6	[0.03]
Normal pulmonary auscultation	41	54.4
SIRS	36	48
Fever (≥38°C)	31	41.3
RV dilatation on echocardiography	34	45.3
Paradoxical septal motion	3	4%
Normal Chest X-ray	41	54.4
Ultrasonography of the legs	35	46.6
Confirmed deep vein thrombosis	8	22.8
Multi organ failure	73	97.3

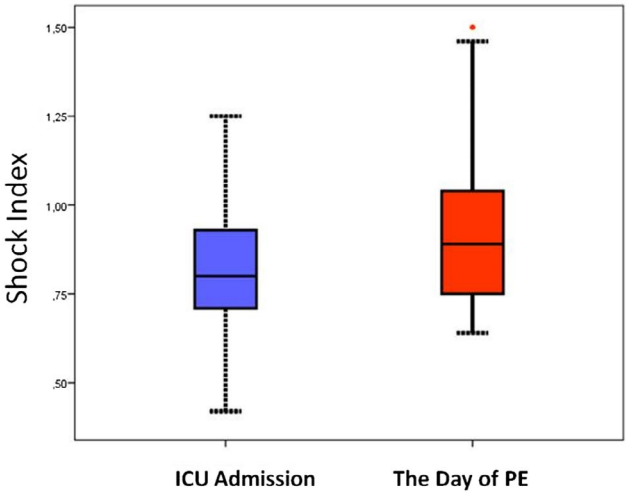

FIGURE 3 Comparison between Shock index (SI) the day of ICU admission and the day of PE development

4 | DISCUSSION

Our findings confirm that subjects in the ICU are at high risk for both DVT and PE, due to the high number of risk-factors. Moreover, our study confirms the results of a few studies recently published, showing a high incidence of PE (ranging from 6 to 20%) in patients requiring ICU admission, despite prophylactic measures.[1-5,17,18]

In addition, we have established—in the current study—that PE is associated with poor outcome. In fact, the development of this complication is associated with a high mortality rate, a high rate of nosocomial infections, and a prolonged ICU and in-hospital length of stay (LOS). Finally, we reveal more than a 5-fold increase in PE incidence in comparison with another study published eight-years ago.[4] In fact, in a previous prospective study conducted in our ICU, the incidence of PE was only 1.9%.[4]

According to the literature, the frequency of PE in ICU patients varied significantly depending on investigation protocols.[18] The apparent increase in PE in our current study (10.1%) and in comparison with our previous study[4] and other published studies[3,8,9,19,20] reporting an incidence ranging from 0.4% to 3%, can be explained by a number of multiple significant factors. First, the severity of the condition of our studied population presenting with high severity scores on ICU admission and requiring invasive MV in 91% of

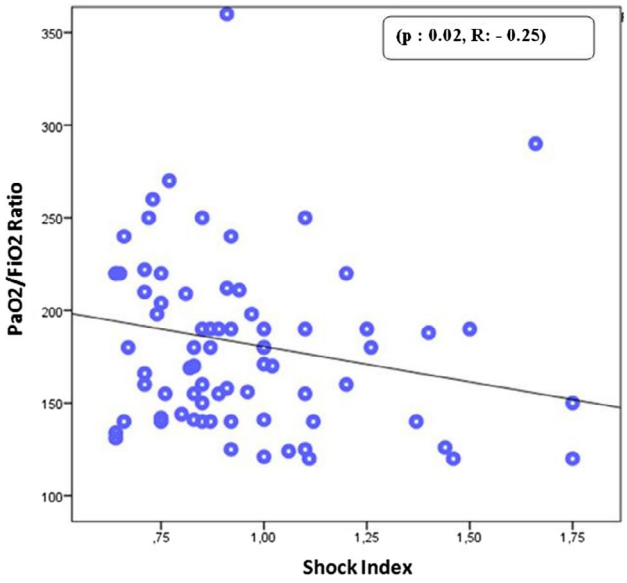

FIGURE 4 Correlation between Shock index (SI) and the PaO2/FiO2 ratio the day of PE development

cases. Indeed, 61 patients (81%) had multi-organ failure on ICU admission. Second, the failure of prophylactic measures, despite the fact that all patients (100%) had received some forms of pharmaceutical prophylaxis (PP) during ICU stay and the use of mechanical prophylaxis were applied in 23 patients (30.7%). Our results invite to revise the preventive dose of unfractionated heparin used (equivalent of 40mg of enoxaparine) in our ICU. Third, the increase in prevalence of PE in our study can be due to the improvement of detection methods and the good experience of our medical team. In our study, all included patients had one or more risk factors of PE (immobility, use of MV, congestive heart failure, chronic obstructive pulmonary disease (COPD), cancer etc.). Furthermore, 51 patients (68%) had a sepsis on ICU admission and 68 (91%) required invasive MV, and 61 (81%) had multi-organ failure (MOF) on ICU admission. In fact, in addition to risk factors for hypercoagulability, incorporating the 3 original Virchow's triad (stasis; endothelial injury and hypercoagulability), severe inflammation observed in patient with sepsis and/or MOF represents a fourth factor for thrombo-embolic complications.[21] In fact, Inflammation increases pro-coagulant factors, and also inhibits natural anticoagulant pathways and fibrinolytic activity, leading to DVT and PE.[22] Indeed, inflammatory process initiated by sepsis may be strained by coexisting tissue hypoxia and systemic inflammation leading to endothelial damages and DVT complications.

In our study, the most frequent cause of ICU admission was polytrauma in 40 patients (53%) with high risk of VTE complications and elevated delay of preventive anticoagulation, due to the possible hemorrhagic events, that can be life-threatening, particularly in patients with head injuries. However, 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 within 24 hours, and at variable intervals thereafter based on clinical manifestations).

The shock index (SI), defined as heart rate (HR) divided by systolic blood pressure (SBP), should be more than 0.8-1.0 in patients with shock, with higher values indicating more severe shock than lower values.[14,23] A shock index (SI) of 1 or more is associated with high mortality.[14,23,24] Currently, the shock index is not included in the standard risk assessment of PE. However, in a retrospective study including 489 normotensive-patients with acute PE between 2006 and 2014, Ozsu S et al[24] showed that shock index and cardiac troponin levels can be safely used together to determine intermediate or high risk in patients with PE. In addition, these investigators postulated that a shock index <1 alone is not a reliable indicator for the treatment of patients in outpatient settings. These authors[24] concluded that an external validation of the present study results in a multicenter cohort is advised to confirm the usefulness of the risk model before using it in clinical practice. In our study, the comparison between SI the day of ICU admission and the day of PE development showed a significant increase of SI the day of PE development (0.85 ± 0.26 vs. 0.95 ± 0.26; $P = .027$). Moreover, we have found a significant association between the Shock index and the PaO2/FiO2 ratio the day of PE development ($P = .02$, $R = -.25$). As a consequence, we think that the usefulness of SI as a reliable indicator for diagnosis and/or the treatment of patients with PE need to be confirmed by large multicenter studies.

In previous studies, PE was associated with higher ICU mortality and a significantly higher ICU LOS.[4,5] Moreover, PE was identified as an independent factor predicting poor outcome.[5] In our study, 38 patients (50.6%) developed nosocomial-infections and 29 (38.6%) died during their ICU stay. Moreover, the multivariate analysis showed that factors associated with a poor prognosis were the presence of Shock the day of PE diagnosis and the presence of RV dilatation on echocardiography. The high mortality rate in our study can be explained by the severity of the patients (91% requiring MV on ICU admission, high severity score on ICU admission, and 61 patients (81%) had one or more organ failure on ICU admission).

There are some limitations to this study that need to be mentioned. Our study suffers from an absence of systematic screening in clinically asymptomatic patients (false negative). Equally, false negative cases of PE and those who died from PE before a CT scan could be performed would have been excluded. In addition, most of our patients were selected on the basis of a positive spiral CT result. Obviously, this excluded patients with PE who did not have a CT scan performed in our ICU, either because PE was not suspected (biased against atypical cases) or where spiral CT-scan was contraindicated (like in cases of acute renal failure). Moreover, despite the fact that positive diagnosis

TABLE 4 Factors associated with a poor outcome in ICU on univariate analysis

	Parameters	Survivors	Non survivors	*P*
On ICU admission	Age (Years)	50.9 ± 18.3	57 ± 17.3	.15
	Sex M/F	39/7	24/5	.82
	SAPS II Score	33.7 ± 11	42.7 ± 10.3	.001
	SAPSIII Score	39.8 ± 12	49.1 ± 11	.001
	Shock index	0.84 ± 0.27	0.87 ± 0.26	.71
	Use of catecholamine	7	13	.002
	Body temperature (°C)	37.4 ± 0.8	37 ± 1.1	.26
The day of diagnosis of pulmonary embolism	Body temperature (°C)	37.7 ± 0.9	37.8 ± 0.7	.67
	Heart rate (beats/min)	108 ± 12	111 ± 15	.45
	Shock (Yes)	5	18	<.001
	Shock index	0.88 ± 0.16	1 ± 0.35	.004
	Use of catecholamine	5	18	<.001
	PaO2/FiO2 ratio	188.6 ± 46	172 ± 56	.18
	pH	7.36 ± 0.05	7.33 ± 0.1	.02
	RV dilatation on echocardiography	14	20	.001
	Mean Prothrombinaemia (%)	74 ± 12	73 ± 14	.58
	Platelets counts (cells/mm^3)	243 239 ± 103 428	221 379 ± 90 381	.34
	Blood Urea (mmol/L)	6.49 ± 0.5	9.23 ± 13	.20
	Blood creatinine (µmol/L)	69.2 ± 46	70 ± 19	.93
	Serum lactate (mmol/L)	1.90 ± 0.43	2.28 ± 0.56	.019
	Troponine (ng/mL)	0.16 ± 0.36	0.91 ± 2.34	.15
	Duration of MV (days)	15.6 ± 11.7	23.3 ± 16.5	.02
	Nosocomial infections	21	17	.41
	ICU stay (days)	25.6 ± 21	27.4 ± 33	.73

of PE was made within 48 hours after ICU admission in 15 patients, no patient was admitted in our ICU for PE. However, we cannot exclude that someone had developed this complication before ICU admission. In fact, PE was not screened for on ICU admission. As a consequence, the late PE may only be a delayed diagnosis.

In conclusion, our findings confirm that subjects in the ICU are at high risk for both DVT and PE, due to a high number of risk-factors. The apparent increase in PE in our current study (10.1%) and a few recent studies in comparison with previous studies can be explained by multiple significant factors, such as the failure of prophylactic measures, the improvement of detection methods and the level of experience of medical teams on this subject. PE was associated with higher ICU mortality and a significantly higher ICU LOS. Our results invite to revise the preventive strategies of DVT and PE in patients requiring ICU admission.

5 | COMPETING INTERESTS

The authors declare that they have no competing interests.

6 | CONSENT FOR PUBLICATION

Not applicable.

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AUTHOR CONTRIBUTIONS

All authors have participated in data collection, data interpretation and mansuscript preparation.

ETHICS

This study was approved by the local ethics committee.

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