Characteristics and clinical management of acute pulmonary embolism in real world: findings from TUSCAN-PE study

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ABSTRACT

Acute pulmonary embolism (PE) remains one of the leading causes of mortality and morbidity in cardiovascular setting. Despite much information about clinical aspects and recommendations or clinical guidelines is available from literature, few data exist about the management of PE in real world of internal medicine scenario. Therefore the aim of the present study was to report on characteristics and management of PE patients admitted in this setting. TUSCAN-PE study was a multicenter, observational, retrospective, cohort study aimed to analyze data of PE patients admitted in Internal Medicine wards of Tuscany. Each center was invited to submit anonymously data of at least ten patients consecutively discharged for acute PE in 2012. Data were referred to demographic, clinical, instrumental, prognostic and therapeutic characteristics. A total of 452 patients from 28 Tuscan centers (60.2% F), with mean age 76.01±12.34 years, were enrolled. A total of 87% of patients was admitted from Emergency Department, but only 65.2% of patients with diagnosis of PE. Around one third of diagnoses of PE was performed by internists. In 14.8% of diagnoses was incidental. In 86% of patients, diagnosis was performed by computer tomography pulmonary angiography. Overall mortality was 9.5%, 5.75% being PE-related. Main risk factors enclosed recent respiratory tract infections (55.3%), immobility (42.25%), recent hospital admissions (33.6%) and cancer (30.3%). In 65.8% of patients, PE was associated with deep vein thrombosis. 16.6% of patients had a shock index ≥1 and 84.75% simplified pulmonary embolism severity index (PESI) score ≥1. A number of 51.5% of patients presented echocardiographic right heart dysfunction, 50.6% and 55.9% of patients presented increased values of troponins and natriuretic peptides, respectively. The following percentage, 6.5%, 71.1% and 22.4%, were defined as high, intermediate and low risk according to the European Society of Cardiology (ESC) criteria, respectively. Antithrombotic treatment was started in Internal Medicine wards in 60.6% of patients. 4.9% of patients were treated with systemic thrombolysis, 15.1% with intravenous unfractionated heparin, whereas low molecular weight heparins and fondaparinux were performed in 39.2% and 39.8% of patients, respectively. Vitamin K antagonists were prescribed in 52.1% of patients at hospital discharge. Fatal and non-fatal major bleedings occurred in 1.7% of patients. TUSCAN-PE study contributes to the knowledge of real life management of acute PE in the Internal Medicine setting.

Introduction

Acute pulmonary embolism (PE) remains one of the leading causes of mortality and morbidity in cardiovascular setting. In the United States, about 150,000 patients per year are diagnosed with acute PE, resulting in thousands of deaths annually.[1] In Italy epidemiological studies estimated a possible incidence of 30-100/100,000 inhabitants/year.[2-4] In Tuscany, one of the most populated regions of Italy encompassing for more than 3.7 million of inhabitants, around 2650 cases of PE were diagnosed in the first six diagnoses of the hospital discharge schedules in 2009 and 1861 diagnosis related groups with number 078 were registered, burdening for 0.40% of overall hospital admissions.[5] Mortality for PE is strictly dependent on hemodynamic compromise at presentation, ranging from less than 3% in normotensive patients without evidence of right ventricular dysfunction (RVD) to up to 30% in patients with shock and up to 70% in pa-

tients with cardiac arrest at presentation.[1] In Tuscany, in 2009 the in-hospital mortality in patients with diagnosis of acute PE was 13.2%, encompassing for 2.1% of overall in-hospital mortality.[5]

Many clinical studies or registries are available for defining clinical characteristics and management of acute PE. However many of these have been performed in the settings of Cardiology, Emergency Medicine or Respiratory Diseases settings, such as the PIOPED I and II, MAPPET, ICOPER, the more recently published IPER and EMPEROR or the oldest PISA-PED.[6-12] Furthermore other studies or registries such as MASTER, RIETE and the ongoing SCOPE, despite enclosing Italian Internal Medicine Units, were conducted in Centers of recognized experience in the field of venous thromboembolism, whereas other studies such as ZATPOL and SWIVTER were conducted in European countries out of Italy.[13-17]

Practical recommendations on prevention, diagnosis, prognostic stratification and acute treatment have had wide diffusion in the last years[18-21] but evidence about their application in real life lack. Therefore the aim of our study was to provide information about characteristics and clinical management of acute PE patients admitted in the setting of Italian Internal Medicine wards.

Materials and Methods

*TU*scan *S*tudy on *C*haracteristics *AN*d clinical management of *P*ulmonary *E*mbolism in internal medicine wards (TUSCAN-PE) study was a multicenter, observational, retrospective, cohort study aimed to evaluate characteristics and clinical management of acute PE patients admitted in Internal Medicine wards of Tuscany affiliated to the Italian Federation of Associations of Hospital Doctors on Internal Medicine (FADOI).

Each center was invited to create a database referred to at least ten patients consecutively discharged for acute PE in 2012. Database was made aimed to provide information about demographic, clinical aspects, outcome, risk factors for venous thromboembolism (VTE), pharmacological prophylaxis before admission, diagnostic tools, prognostic stratification, therapeutic management and its bleeding complications during hospital stay. Data were collected in the first three months of 2013 and accordingly submitted to head Center, that provide for final analysis.

Results

A total of 452 patients from 28 Internal Medicine Units representatively allocated over the whole Tuscany (Figure 1) (60.2% F), with mean age 76.01±12.34 years, were enrolled. General characteristics of patients

are summarized in Table 1. Fifteen Centers were affiliated to primary non-academic Hospitals, 9 Centers to secondary non-academic Hospitals and 4 Centers to tertiary academic Hospitals.

A percentage of 87% of patients was admitted from Emergency Department, 8% from Cardiology or Intensive wards, 2% from surgical wards and 3% from other hospital wards. 67.9% of patients (65.2% of those admitted from Emergency Department) was admitted with main diagnosis of PE, whereas 32.1% of patients (34.8% of those admitted from Emergency Department) was admitted with another diagnosis and the diagnosis of PE was performed by Internists. The main alternative diagnoses are showed in Table 2. The mean time from hospital arrival to confirmed diagnosis of PE was 1.34±3.70 days (range 0-51 days). In patients in whom Internists made diagnosis of PE, the mean time from hospital admission to confirmed diagnosis was 2 days (mean 3.15±3.90 days, range 0-30 days). In patients in whom diagnosis of PE was searched and made by Internists, the mean time from hospital admission to diagnosis was 1 day. In 78.5% of patients, diagnosis was performed by computer tomography pulmonary angiography (CTPA) scan alone, in 5.1% by using scintigraphy lung scan alone, in 7.5% by combination of CTPA and scintigraphy lung scan. In 8.9% of patients diagnosis was performed based on clinical suspicion associated with detection of deep vein thrombosis at legs ultrasonography and/or echocardiographic or biomarkers signs of right heart dysfunction. A percentage
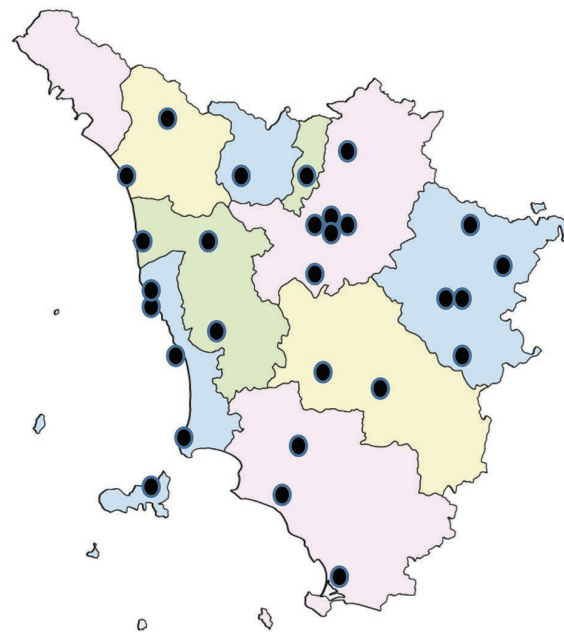

Figure 1. TUSCAN-PE Centers.

of 14.8% of PE diagnoses was incidental, 22.6% when performed by internists. In patients in whom diagnosis of PE was performed by CTPA, 49.6% of thromboemboli were central (main pulmonary or its branches), 20.8% lobar, 29.6% segmental or sub-segmental. In 61.5% of cases PE was bilateral. In patients in whom PE was found by scintigraphy lung scan, 76% of cases presented 2 or more perfusion defects. Legs ultrasonography was performed in 83.6% of patients. In 65.8% of patients, a deep vein thrombosis (DVT) was found, 45.2% proximal and 20.6% distal. DVT was bilateral in 16.8% of patients.

Recent (within 3 months) respiratory tract infections (55.3%), immobility (42.25%), hospital admissions within the last three months (overall 33.6%, medical setting 25.8%, surgical setting 7.8%) and cancer (30.3%) were the main risk factors for VTE. Figure 2 summarizes the risk factors for VTE. 33% of patients performed VTE prophylaxis before hospital admission, 13.1% full prophylactic dose of low molecular weight heparins (LMWHs) or fondaparinux, 15.6% reduced prophylactic dose of LMWHs or fondaparinux, 4.2% vitamin K antagonists (2.2% under dosed). All-cause mortality was 9.5%, whereas 5.75% was PE-related. A percentage of 16.6% of patients had a severity index (SI) ≥ 1. All-cause mortality was 6.10% (3.70% PE related) in patients with SI <1 *versus* 25.30% (17.30% PE related) in patients with SI ≥ 1. 84.75% of patients had a simplified pulmonary embolism shock index (sPESI) score ≥ 1. All-cause and PE-related mortality were 0% in patients with sPESI score 0, whereas 10.95% and 5.75% were respectively in patients with sPESI score ≥ 1.

Trans-thoracic echocardiogram, natriuretic peptides [brain natriuretic peptide (BNP) or its terminal portion (NT-proBNP)] and troponins assays were performed respectively in 70.1%, 35.6% and 80.7%. 51.5% of patients undergone to trans-thoracic echocardiography showed RVD, whereas 50.6% and 55.9% of patients respectively undergone to BNP/NT-proBNP and troponins assays presented increased values of these. The European Society of Cardiology (ESC) criteria defining patients in high, intermediate and low early mortality risk were applicable to 78.4% of patients.[18] Figure 3 shows the early mortality risk distribution according to ESC criteria and in-hospital mortality according to these in the analyzed patients. Antithrombotic treatment was started in Internal Medicine wards in 60.6% of patients. A percentage of 4.9% of patients underwent intravenous thrombolysis, 15.1% to intravenous unfractionated heparin, whereas LMWHs and fondaparinux were performed in 39.2% and 39.8%, respectively. In 1.1% of patients, a vena cava filter was placed. Table 3 shows the acute treatment according to early mortality risk assessed by ESC criteria. Treatment related bleedings occurred in 3.1% of patients, 0.2%

being fatal, 1.5% major and 1.4% non-major. Table 4 summarizes bleeding complications.

At hospital discharge, vitamin K antagonists were prescribed in 52.1% of patients, whereas LMWHs and fondaparinux were prescribed in 24.9% and 21.8% of patients, respectively.

Table 1. General characteristics.

Patients number	452
Males/Females	180/272
Mean age (years)	76.01±12.34
Males	73.55±12.45
Females	77.65±12.02
Over 75 years	62.70%
Over 85 years	28.1%
Mean hospital stay (days)	10.60±6.63
In-hospital mortality	
Overall	9.50%
PE related	5.75%
VTE prevention before admission	33%
Full prophylactic dose LMWHs or fondaparinux	13.1%
Reduced prophylactic dose LMWHs or fondaparinux	15.6%
VKAs	4.2%
Under dosed	2.2%
In range	1.5%
Over dosed	0.5%
Mean heart rate (beats for minute)	92.37±20.26
Mean systolic blood pressure (mmHg)	127.45±24.36
Mean PaO$_2$ (mmHg)	63.7±13.8
Renal failure	
Moderate (CrCl 30-50 mL/min)	20.6%
Severe (<30 mL/min)	6%

PE, pulmonary embolism; VTE, venous thromboembolism; LMWHs, low molecular weight heparins; VKAs, vitamin K antagonists.

Table 2. Main alternative diagnoses at hospital admission.

Pulmonary embolism mimics	64.3%
Pulmonary infiltrate	14.7%
Pleural effusion	14.7%
Respiratory failure	10.4%
Heart failure	7.8%
Syncope	6.1%
Chest pain	2.6%
Chest pain associated with syncope	1.7%
Fever	1.7%
Deep vein thrombosis as main diagnosis	10.4%
Other diagnoses	25.3%

Discussion

Acute PE in one of the most feared diseases to manage in Internal Medicine wards, due to high mortality and morbidity. Prevention, diagnosis, prognostic stratification and treatment represent the mainstays of its hospital management and remain challenges for physicians. The burden of VTE, of which PE represents the most feared manifestation, is so severe in acutely ill medical patient that to date around 75% of the diagnoses of VTE in hospitalized patients is referred to medical patients and 75% of VTE-related deaths occurs in this kind of subjects.[22-26] Despite recommendations on PE management are worldwide widespread, literature data on how physicians translate these in real practice lack. Therefore studies aimed to give information about real life management of acute PE are warranted. TUSCAN-PE study aimed to give answers about it in the context of Internal Medicine wards of Tuscany.
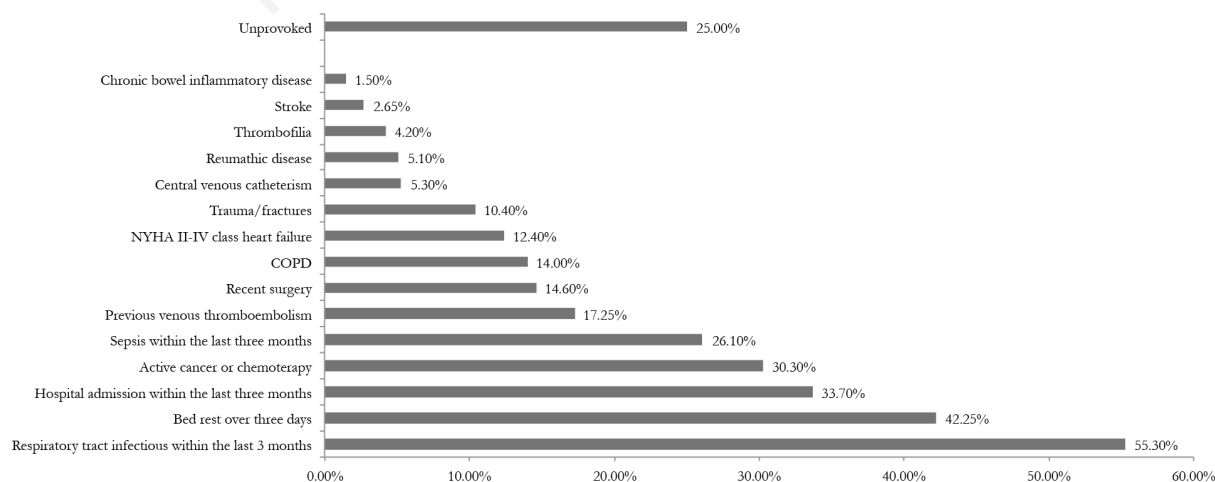
Findings from our study demonstrates that the PE population discharged from Internal Medicine wards is very old, more than 60% being 75 years-old and older and around 30% 85 years-old and older. Compared with other studies, the population of TUSCAN-PE is older, even when considered other Italian populations enrolled in registries, such as those of IPER, an Italian registry

performed in 49 Centers of which 37 Cardiology Units, 6 Emergency Medicine Units and 6 Internal Medicine Units, and RIETE, an international multicenter registry.[6-14,27] One of the most important findings emerged in TUSCAN-PE study was that around one third of patients received diagnosis of PE from Internists in the first hours from admission in their wards. Diagnosis of acute PE remains a challenge due to non-specific presentation in terms of signs, instrumental and laboratory findings, especially in the older patients such as those of our study.[28] Physicians should increase their efforts to reduce misdiagnoses and diagnostic delays. Clinical suspicion should be the *primum movens* for diagnosis of acute PE and the estimation of pre-test probability (PTP) by using validated tools, such as Wells or Geneva scores, may rise it. Therefore their use in clinical practice should be encouraged.[29,30] CTPA is now recognized as the main and most available diagnostic tool to rule in the diagnosis of acute PE.[18-20] Strategies based on likely PTP and/or positive D-dimer identify patients undergoing CTPA or scintigraphy lung scan aimed to rule in the diagnosis of PE.[18-20] Legs ultrasonography permits to detect DVT which represents the major font of PE.[18-20] Legs ultrasonography could be enclosed in the diagnostic work-up of PE, since than the presence of proximal DVT in patients with likely PTP scoring may

Table 3. Treatment according to European Society of Cardiology criteria-based mortality risk.

	High risk (%)	Intermediate risk (%)	Low risk (%)
rtPA	13.6	6.4	1.2
UFH	27.7	17.2	15.1
LMWH or fondaparinux	58.7	76,4	83.7

UFH, unfractionated heparin; LMWH, low molecular weight heparins.

Figure 2. Risk factors for venous thromboembolism. COPD, chronic obstructive pulmonary disease.

rule in indirectly the diagnosis and conclude the diagnostic process.[18-20] Our study demonstrates that to date CTPA is the most widespread diagnostic tool for PE, whereas only few patients undergo scintigraphy lung scan. These findings agree with those of most recent studies.[10,11] Moreover our study demonstrates that legs ultrasonography for DVT detecting is routine practice in Internal Medicine.

The main risk factors for VTE in ill medical patients are represented by stroke, heart failure, cancer, chronic obstructive pulmonary disease associated with respiratory failure (especially when requiring mechanical ventilation), acute myocardial infarction, sepsis, rheumatic and chronic inflammatory bowel diseases. The risk increases significantly when these conditions occur in elderly subjects aged >75 years, in patients with impaired mobility, those with a history of previous VTE and those with inherited or acquired thrombophilia.[22,31-34] In TUSCAN-PE recent infectious diseases, especially affecting the respiratory system, were found as the main risk factors of PE. Despite this percentage is much greater compared to the most recently published studies on topic,[10,11,14,17] this finding is not completely surprising, since than in the recent

years many literature reports have focused on link between infectious diseases, inflammation and thrombosis.[35,36] Further investigations are warranted to better define the role of infectious diseases as risk factors for PE. Immobility remains one of the most frequent risk factors for VTE, especially in elderly patients and our study confirms it in agreement with literature.[9-14,17,28]

In TUSCAN-PE around one third of patients discharged with PE from Internal Medicine wards has active cancer. This finding is higher compared to the most

Table 4. Treatment related bleedings.

Overall	3.1%
Fatal bleedings (brain)	0.2%
Non-fatal major bleedings	1.5%
Brain	0.2%
Retroperitoneal	0.2%
Gastro-intestinal	1.1%
Non-major bleedings	1.4%
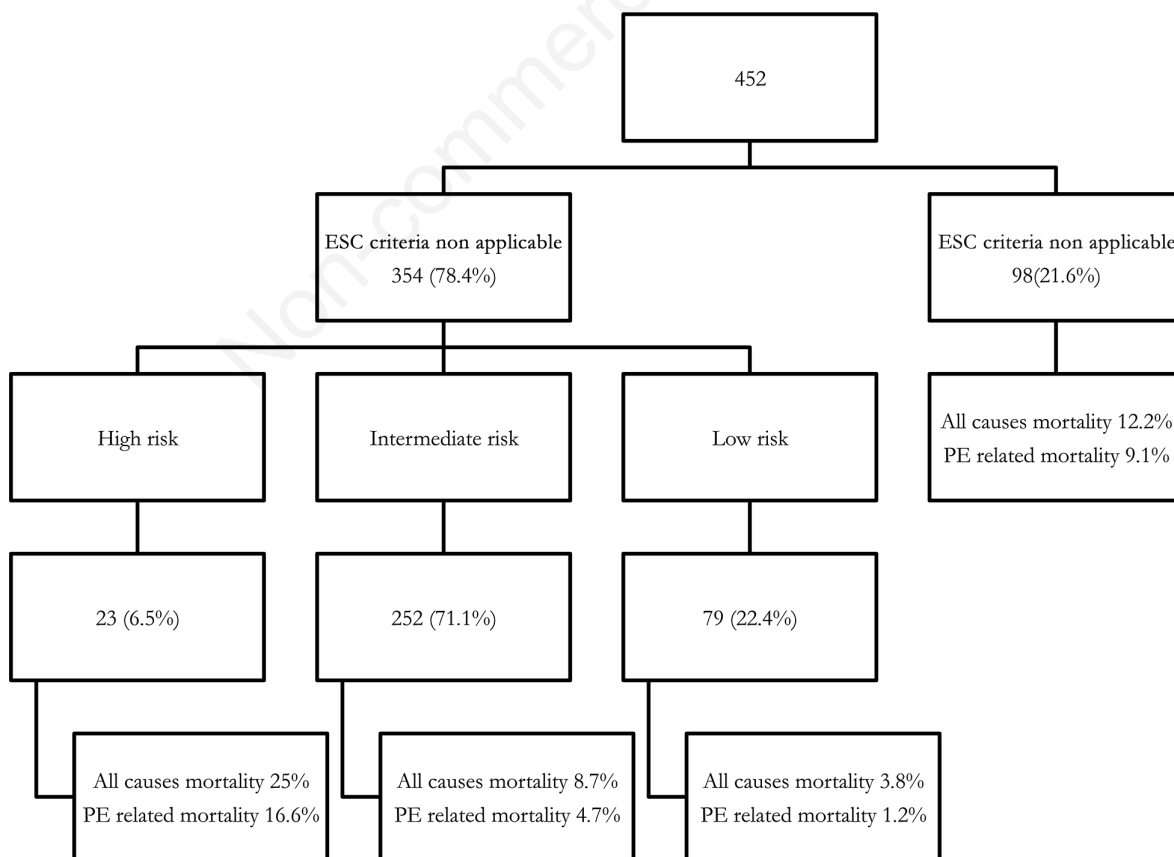
Figure 3. Risk stratification according to European Society of Cardiology (ESC) criteria. PE, pulmonary embolism.

recent studies, such as IPER, EMPEROR, MASTER, SWIVTER and ZATPOL, but similar to that observed in the Italian population of RIETE registry.[10,11,13,16,17,27] This could be ascribed to higher mean age of patients enrolled in our study other than a possible major selection of patients admitted in non-Internal Medicine settings, such as those of the abovementioned studies.

Recent hospitalization as possible risk factor for VTE was already underlined from Spencer *et al.* in 2007 in the United States and more recently has been found in the EMPEROR and SWIVTER studies.[11,17,37] In the study of Spencer *et al.*, the burden of recent hospitalization in surgical or medical settings was similar, whereas in our study 76.7% of patients with PE who had been recently admitted to hospital were in medical setting. In the EMPEROR study 23.8% of patients with PE had been recently hospitalized, but it's unclear the setting of hospitalization.[11]

Randomized controlled trials have clearly demonstrated the efficacy and safety of pharmacological prophylaxis in ill medical patient.[22,38-40] A meta-analysis of literature evidence demonstrated that VTE pharmacological prophylaxis during hospital stay in ill-medical patients significantly reduces the incidence of DVT, non-fatal and fatal PE during hospital stay without increasing the risk of major bleeding, but any advantage on overall mortality was found.[41] Studies aimed to analyze the role of extended pharmacological prophylaxis in ill medical patients have found a low risk/benefit ratio due to not acceptable rate of bleedings compared to placebo.[42-44] Therefore the most recent guidelines suggest to avoid prolonged pharmacological thromboprophylaxis in ill medical patients beyond two weeks.[45] However, as seen, the recent hospitalization as possible risk factors for PE is a cumbersome problem. Avoiding to prolong prevention could be a risk in subgroups of patients, such as patients suffering from respiratory tract infections or sepsis or confined to bed. In the SWIVTER study 58% of patients developing VTE episodes during or shortly after hospitalization had received prophylaxis, these findings being similar to those observed in our study.[46] Therefore extended prophylaxis and its dose should be tailored on single patient. In TUSCAN-PE in fact many patients with acute PE were on pharmacological prophylaxis at hospital arrival, even if at lower doses in one half of patients undergone to pharmacological prophylaxis despite moderate or severe renal failure were found only in 26% of this subgroup. In 2008 ESC suggested to divide PE patients in three classes at different early mortality risk based on hemodynamic compromise at presentation.[18] Patients with acute PE presenting with cardiac arrest, shock [systolic blood pressure (SBP) ≤90 mmhgHg] or a drop of 40 mmHg in SBP respect the usual for at least 15 min were defined as high risk being early mortality in these

patients higher than 15%, whereas normotensive patients with signs of RVD or increased troponins as sign of myocardial damage were defined at intermediate risk, early mortality ranging from 15% to 3%, and finally normotensive patients without RVD or myocardial damage were defined at low risk, early mortality being lower than 1%.[18] ESC suggested that acute treatment should be tailored on the basis of early mortality risk. Therefore in acute phase of treatment, high risk patients should receive intravenous thrombolysis if not contraindicated or embolectomy, whereas intermediate risk patients and low risk patients should receive unfractionated heparin (UFH), LMWHs or fondaparinux. LMWHs or fondaparinux should be preferred over UFH with the exception of patients with severe renal failure. Oral anticoagulation with vitamin K antagonists (VKA) should be overlapped to parenteral anticoagulants starting from the first day.[18] In low risk patients, ESC recommendations suggested early hospital discharge or at home treatment.[18] ESC criteria were derived from available literature in that moment and on Expert consensus, but a validation from clinical trials was lacking.[18]

Prognostic stratification of early risk mortality is therefore of utmost importance.[47] Other than ESC criteria, prognostic stratification could be performed by using clinical parameters or clinical scoring, such as the SI or the sPESI.[47,48] SI consider the ratio between heart rate (HR) in beat for minutes (bpm) and SBP in mmHg. High risk of early mortality is defined by SI≥1.[47] The sPESI score considers variables associated with early mortality risk and derived from multivariate analysis, such as age over 80 years, history of cancer, heart failure and/or chronic obstructive pulmonary diseases, HR>110 bpm, SBP<100 mmHg, arterial oxygen saturation (SaO_2) <90% or arterial oxygen partial pressure (PaO_2) <60 mmHg. sPESI score ranges from 0 to 6. In the validation cohort, early mortality rate was lower than 1% in patients with sPESI score 0 and higher than 10% in patients with sPESI score ≥1.[48]

Despite data were collected retrospectively, our study highlights the importance of prognostic stratification of acute PE in clinical practice. ESC criteria, SI and sPESI permit to stratify prognosis of PE in real life. Our study in fact validated the ESC criteria in real practice, as more recently occurred with the IPER study.[49] In-hospital mortality rates in fact fell into those speculated from ESC recommendations.

Our study found that SI really identified high mortality risk patients, but unfortunately it didnot identify low risk patients. Therefore it may be used to select patients needing for closer monitoring and more aggressive therapy but it should not be used alone for identifying patients candidate to early discharge or at home treatment.

Finally our study contributes to the external vali-

dation of the sPESI as prognosticator. Our study confirms that sPESI is highly sensitive to identify low risk patients. Patients with sPESI score 0 in fact had an in-hospital mortality rate of 0%. Therefore sPESI may be an optimal instrument to identify patients candidate for early hospital discharge or at home treatment.

Our study highlights the low percentage (4.9%) of patients undergone to systemic thrombolysis despite high early mortality risk. In the IPER study, 11% of patients underwent to systemic thrombolysis, but it reached 40% in unstable patients *versus* 13.6% in this kind of patients in our study.[10] In the SWIVTER study 3.3% of patients underwent to systemic thrombolysis, whereas in the EMPEROR study systemic thrombolysis was performed in 2.3% of patients.[11,17] The reason for the underuse of thrombolysis may be ascribed to the fear of bleeding complications in an old and fragile population such as that admitted in Internal Medicine wards, even if advanced age alone should not be considered as a contraindication for this treatment option. High prevalence of immobilized and cancer patients encountered in our study may define a fragile population.

Our study demonstrates that invasive procedures such as pulmonary embolectomy or vena cava filter placement, despite recommended as emergency procedure in patients with absolute contraindication to anticoagulation or in the case of embolectomy not responding to it, are rarely performed, probably due to the lack of availability, especially in most peripheral or non-academic Centers.[18,19,50]

On the other side our study highlights the high percentage of patients treated with LMWHs or fondaparinux in acute phase, even if in high risk patients, performed in more than 80% of overall patients, in agreement with literature evidence.[10,11,14,16] Surprisingly, around one half of our patients were discharged without switching to oral anticoagulation. However, it is not possible to know if this kind of therapy has been started after hospital discharge due to the lack of follow-up. The main limitations of vitamin K antagonists, especially in elderly patients, such as unpredictable pharmacological profile and narrow therapeutic window requiring routine laboratory monitoring, slow onset and offset of action, multiple drug and food interactions and the fear of bleeding complications may make physicians reluctant to use VKA. These findings agree with those of RIETE registry agree, demonstrating that parenteral anticoagulation seems to be the choice treatment option in very old patients, such as nonagenarians.[51]

The marketing of new oral anticoagulants, safer and easier to use in the acute phase of PE, may increase the percentage of patients switched to oral anticoagulation, but to date literature evidence on real life management of PE in the era of new oral anticoagulants lacks.[52]

Treatment related bleedings represent an independent risk factor of mortality in acute phase of PE.[53] The prevalence of bleedings in our study agrees with literature evidence.[10-14,16,17]

Conclusions

The approach to diseases in real world is of utmost importance for planning care. TUSCAN-PE focuses on real life management of acute PE in Internal Medicine wards of Tuscany, independently from hospital level and grading of expertise on this topic. Findings from TUSCAN-PE study demonstrate that: i) diagnosis of PE remains a challenge; ii) some risk factors such as respiratory infectious diseases and sepsis are emerging; iii) recent hospitalization in medical setting may represent a trigger for the development of procoagulative mechanisms which lead to PE despite pharmacological prophylaxis; iv) prognostic stratification allows to define the early mortality risk; but v) treatment is far to be tailored on it due to frailty of patients in the setting of Internal Medicine wards. Prospective studies are warranted to better define these findings.

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