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Delayed Diagnosis in Pulmonary Embolism: Frequency, Patient Characteristics, and Outcome

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Keywords
Pulmonary embolism · Delayed diagnosis · Characteristics · Mortality

Abstract
Background: The incidence and the outcomes of pulmonary embolism (PE) missed during emergency department (ED) workup are largely unknown. ***Objectives:*** To describe the frequency, demographics, and outcomes of patients with delayed diagnosis of PE. ***Methods:*** We retrospectively compared patients diagnosed with PE during ED workup (early diagnosis) with patients diagnosed with PE thereafter (delayed diagnosis). Electronic health records (EHR) of 123,560 consecutive patients who attended a tertiary hospital ED were screened. Data were matched with radiology and pathology results from the EHR. ***Results:*** Of 1,119 patients presenting to the ED with early workup for PE, PE was diagnosed in 182 patients (80.5%) as early diagnosis. Delayed diagnosis was established in 44 cases (19.5%) using radiology and/or autopsy data. Median age of patients with early diagnosis was significantly lower as compared to delayed diagnosis (67 vs. 77.5 years). Main symptoms were dyspnea (109 patients [59.9%] in early, 20 patients [45.5%] in delayed diagnosis), chest pain (90 patients [49.5%] in early, 8 patients [18.2%] in delayed diagnosis), and nonspecific complaints (16 patients [8.8%] in early, 13 patients [29.5%] in delayed diagnosis). In-hospital mortality was 1.6% in early diagnosis and 43.2% in delayed diagnosis. ***Conclusions:*** Delayed diagnosis of PE carries a worse prognosis than early diagnosis. This discrepancy may arise from either delayed therapy, confounding variables (e.g., older age), or both. Possible reasons for delayed diagnoses are nonspecific presentations and symptoms overlapping with preexisting conditions.

Introduction

Venous thromboembolism is a frequent condition with an overall incidence of 100–200/100,000 population [1, 2]. Acute pulmonary embolism (PE), the clinically most severe form of venous thromboembolism, is a potentially fatal condition if not diagnosed and treated in time [3]. PE is also a major cause for morbidity and medical resource use, such as hospitalization [4]. Older patients presenting to the

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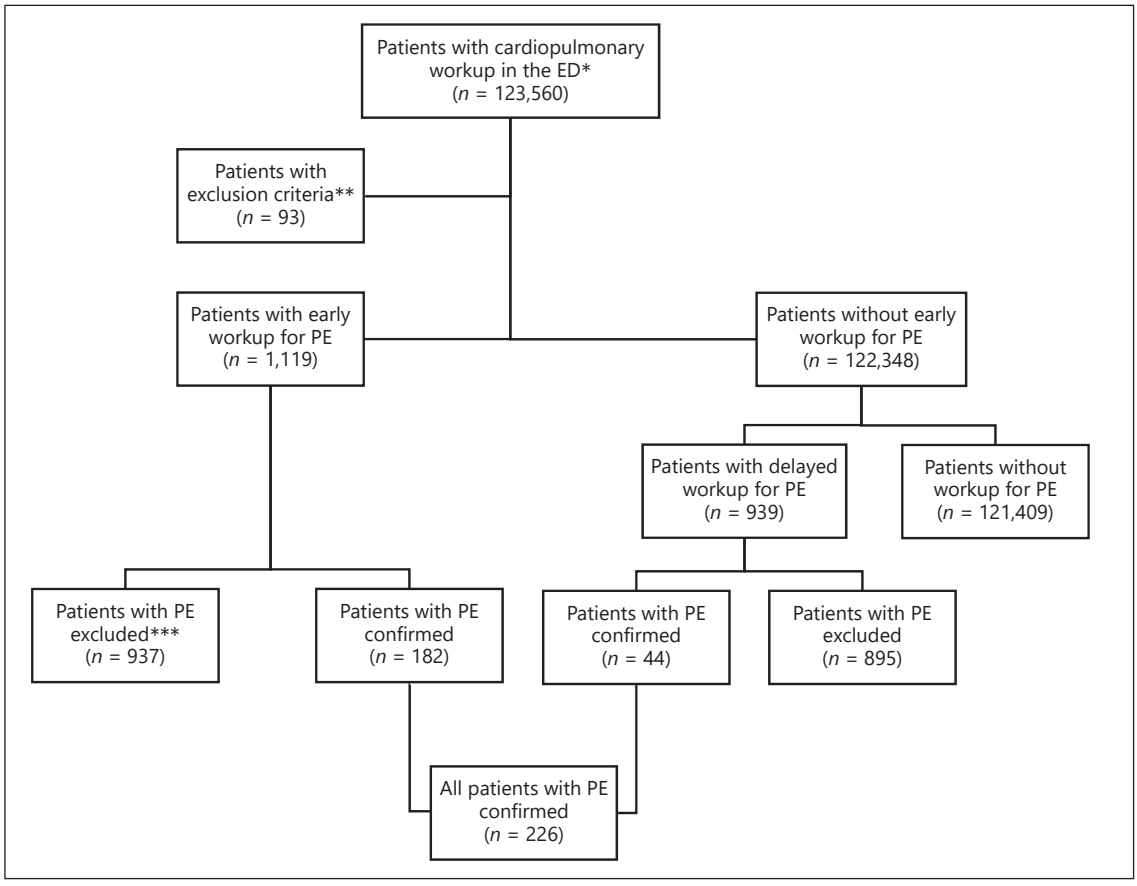

Fig. 1. Flowchart of inclusion. * Patients were included if any cardiology or pulmonary workup was performed in the ED. ** Patients were excluded if they were referred (n = 33), were previously diagnosed (n = 26), had PE provoked by inpatient therapy (n = 13), were fast tracked (n = 12), PE was diagnosed after 30 days (n = 3), cause of death was changed after secondary review of the autopsy data (n = 3), or if relevant data was missing (n = 3). *** Patients were excluded after negative CTPA (n = 930) or SPECT (n = 7).

emergency department (ED) with acute dyspnea and respiratory failure have an 18% probability of PE [5].

Dyspnea and chest pain are the 2 most common symptoms associated with PE [6, 7]. However, in "clinically unsuspected" PE, dyspnea and chest pain are less frequently present [8]. Further, nonspecific complaints such as generalized weakness, feeling exhausted, and recent falls – frequent in older patients – have been observed in PE as well [9, 10]. The true incidence of PE is difficult to determine [11, 12] as delayed or missed diagnoses are common. This may be due to the wide range of presenting symptoms, including cardiogenic shock and sudden death. Commonly used clinical diagnostic scores, such as the Wells or the Revised Geneva Score, are doubtlessly helpful in patients with typical presentation, but their usefulness in patients presenting with nonspecific complaints might be limited.

Depending on the severity of PE, case fatality rates range from 1.2% up to 59% [4, 13–17], the only randomized study showing a short-term mortality of 26% in untreated PE [18]. Although risk factors and clinical features have been described in delayed diagnosis of PE [3, 19–23], outcomes in patients with PE missed during ED workup are unknown. Therefore, the aim of this study was to describe the frequency, characteristics, and mortality in patients admitted through the ED with delayed diagnoses of PE.

Methods

Study Design and Population

This study was designed as a single-center retrospective study using electronic health records (EHR) from the University Hospital of Basel, Switzerland (UHBS), between January 1, 2011 and De-

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cember 31, 2013. The UHBS is an urban tertiary-care hospital with about 50,000 ED visits per year. The study protocol was approved by the local Ethics Committee; informed consent was waived due to sample size and the retrospective nature of the study (EKNZ 2014-183). This study is reported according to the STROBE guidelines, is in accordance with the Declaration of Helsinki, and is registered at www.clinicaltrials.gov, NCT02476721.

Patients, 18 years or older, who received any cardiology workup (at least an ECG) or any pulmonary workup (at least a chest X-ray) in the ED were screened for inclusion (Fig. 1). Patients were excluded if (1) they were referred with a suspicion of PE by other departments of our institution, other hospitals, or healthcare providers, (2) PE was radiologically diagnosed before presentation, (3) PE was provoked by inpatient therapy (e.g., trauma room resuscitation, intensive care, surgery, or other invasive procedures), (4) they were fast-tracked (direct admission to internal medicine or direct transfer to catheter lab), (5) they were diagnosed with PE after the 30-day follow-up, (6) cause of death was changed after secondary review of the autopsy data, or (7) relevant data was missing. To identify all patients with a clinical suspicion of PE, EHR were screened in all eligible patients by electronically cross-referencing them with radiology and autopsy EHR up to 30 days following presentation. All computed tomography, chest X-ray, lung perfusion scan, echocardiography, and autopsy reports concerning PE were identified. Reports were searched for the following keywords: thromboembolism or thrombo-embolism, pulmonary embolism, pulmonary artery occlusion, and pulmonary infarction. These reports were studied independently by 2 researchers regarding diagnosis or exclusion of PE. A detailed chart review was performed using 9 out of 12 methodological items recommended for medical record review studies [24, 25]. In case of disagreement, a third reviewer was asked to make an independent decision – thereafter, a final consensus-based decision was made. Double data entry of chart reviews was performed using Microsoft Access 2010.

Outcomes and Measurements

The primary endpoint of this study was the occurrence of PE at early and delayed workup. The secondary endpoint was in-hospital mortality within 30 days in patients with PE confirmed at early and delayed workup. PE was defined as either (1) evidence for multiple regional perfusion deficits in single proton emission computed tomography (SPECT scintigraphy using 99m technetium), (2) at least segmental artery perfusion deficit in CTPA, (3) signs of acute right ventricular stress, dilation, or dysfunction (estimation of right ventricular function was performed using tricuspid annular longitudinal excursion, peak systolic velocity of tricuspid annulus, right ventricular fractional area change, and the elevation of pulmonary artery pressure was detected measuring tricuspid regurgitate jet velocity plus an estimation of right atrial pressure by assessment of the inferior vena cava 2 cm proximal to the right atrium) [26] by bedside echocardiography in critically ill patients, (4) clinical signs of PE, such as acute dyspnea in the presence of deep vein thrombosis, and (5) embolism diagnosed at autopsy.

Early diagnosis was defined as PE confirmed during early workup in the ED (within 24 h after presentation). Delayed diagnosis was defined as PE confirmed by imaging or autopsy during delayed workup (between 24 h and 30 days after ED presentation), except for cases undergoing subsequent surgery or other procedures unrelated to the primary reason of presentation; these were diagnosed as "PE provoked by treatment" and subsequently excluded, as described above. Further, delayed workup was divided into "early delayed" (24 to 96 h after ED presentation) and "late delayed" (96 h to 30 days after ED presentation) workup.

Patients with early workup for PE in the ED were defined as cases with (1) a matching keyword as defined above in the EHR, or (2) a matching keyword in electronic radiology records. If PE was diagnosed as described above, patients were categorized as "PE confirmed," if PE was excluded by one of the methods described, they were categorized as "PE excluded."

Patients without initial clinical evidence for PE in the ED were defined as cases with (1) no match of the following keywords in the EHR: thromboembolism or thrombo-embolism, pulmonary embolism, pulmonary artery occlusion, and pulmonary infarction, and (2) an uneventful 30-day follow-up.

The ED diagnoses of patients with PE confirmed at delayed workup (as defined above) were retrieved from the EHR, and categorized according to the ICD-10 system (German modification, version 2016, updated December 21, 2015). Coding was performed by professional medical encoders.

Nonspecific complaints were defined as all complaints that are not part of the set of specific complaints (e.g., chest pain, dyspnea) or signs or where an initial working diagnosis cannot be definitively established as previously described [10].

For long-term follow-up, patients were followed up to 3 years after index presentation. Data were analyzed using EHR from our hospital. Patients lost to follow-up were counted as deceased.

Statistics

For statistical analyses, R version 3.6.1 was used. Descriptive statistics are presented as counts and frequencies for categorical data, and mean (SD) and median (interquantile range, IQR) for metric variables. For comparisons between early and delayed PE diagnosis in normally distributed values, *t* tests, and in non-normally distributed values, Kruskal-Wallis, chi-square, or exact Fisher's tests (when expected frequencies were <5) were used as appropriate. A p value <0.05 was considered significant.

Results

Screening for cardiac or pulmonary workup between January 1, 2011 and December 31, 2013 yielded 123,560 ED patients, 9,135 did not undergo cardiopulmonary workup. Ninety-three patients were excluded for not meeting the inclusion criteria (33 referrals from other hospitals, 26 previously diagnosed PE, 12 fast-tracked patients, 13 PE provoked by inpatient therapy, 3 PE diagnosed >30 days after ED presentation, 3 causes of death were changed after secondary review of the autopsy data, relevant data missing in 3 patients). Of the remaining 123,467 patients, 1,119 patients had early workup for PE. In this group, PE was confirmed in 182 patients (by CTPA in 161 patients, by SPECT in 17 patients, by clinical signs of PE in the presence of deep vein thrombosis in 3 patients, and by bedside echocardiography in 1 pa-

Table 1. Patient characteristics and outcomes

	All PE (n = 226)	Early workup (n = 182)	Delayed workup (n = 44)	Early delayed workup (n = 14)	Late delayed workup (n = 30)	p values*
Sex, male	124 (54.9)	99 (54.4)	25 (56.8)	6 (42.6)	19 (63.3)	0.90
Age, years	68.5 (56–80)	67 (54.3–77)	77.5 (66.8–83.3)	79 (70.8–85.8)	75.5 (66.3–81.8)	<0.001
COPD	21 (9.3)	16 (8.8)	5 (11.4)	2 (14.3)	3 (10)	0.570
Dyspnea**	129 (57.1)	109 (59.9)	20 (45.5)	10 (71.4)	10 (33.3)	0.117
Chest pain**	98 (43.4)	90 (49.5)	8 (18.2)	4 (28.6)	4 (13.3)	<0.001
Nonspecific complaints	29 (12.8)	16 (8.8)	13 (29.5)	5 (35.7)	8 (26.7)	<0.001
D-dimer testing	132 (58.4)	129 (70.9)	3 (6.8)	1 (7.1)	2 (6.7)	<0.001
Echocardiography	82 (36.3)	59 (32.4)	23 (52.3)	12 (85.7)	11 (36.7)	0.002
Signs of right heart strain (% of patients with echocardiography)	32 (39)	23 (39)	9 (39.1)	5 (41.7)	4 (36.4)	0.274
Caval thrombosis	2 (0.9)	2 (1.1)	0 (0)	0 (0)	0 (0)	1.000
Chest CT	185 (81.9)	161 (88.5)	24 (54.5)	10 (71.4)	14 (46.7)	<0.001
Pulmonary infarction on CT	42 (18.6)	38 (20.9)	4 (9.1)	4 (28.6)	0 (0)	0.112
Anticoagulant therapy	209 (92.5)	181 (99.5)	28 (63.6)	13 (92.6)	15 (50)	<0.001
Thrombolytic therapy	4 (1.8)	4 (2.2)	0 (0)	0 (0)	0 (0)	1.000
ICU care	30 (13.3)	22 (12.1)	8 (18.2)	5 (35.7)	3 (10)	0.411
In-hospital mortality	22 (9.7)	3 (1.6)	19 (43.2)	3 (21.4)	16 (53.3)	<0.001

Values are presented as n (%) except for age, which is median (IQR). * Comparison between early and delayed workup. ** One patient may present with several symptoms.

tient). PE was excluded in 937 patients of the early workup group using CTPA in 930 patients and SPECT in 7 patients. Delayed workup was made in 939 patients. Among these, PE was diagnosed in 44 patients (in 24 patients by CTPA, in 4 patients by SPECT, and in 16 patients by autopsy). Overall, PE was diagnosed in 226 patients using health record and autopsy data (182 patients [80.5%] as early and 44 patients [19.5%] as delayed diagnosis; Fig. 1).

As shown in Table 1, patients with PE diagnosed at early workup were significantly younger than patients with PE diagnosed at delayed workup. The main presenting symptoms in early diagnosis of PE were dyspnea in 109 patients (59.9%) and chest pain in 90 patients (49.5%). In the delayed PE diagnosis group, 20 patients (45.5%) presented with dyspnea, 8 patients (18.2%) with chest pain, and 13 patients (29.5%) with nonspecific complaints.

PE was diagnosed by chest CT in 161 patients (88.5%) at early workup and in 24 patients (54.5%) at delayed workup, showing pulmonary infarction in 38 patients (20.9%; early workup) and in 4 patients (9.1%; delayed workup). Echocardiography was performed in 59 patients (32.4%) at early workup and in 23 patients (52.3%) at delayed workup, showing signs of right heart strain in 23 patients (39%; early workup) and 9 patients (39.1%; delayed workup). Caval thrombosis was diagnosed in 2 patients (1.1%) in the early workup group. D-dimer testing at the ED was significantly less frequent in patients with delayed diagnosis (3 patients, 6.8%) than in early diagnosis (129 patients, 70.9%).

With the exception of 1 patient, who was diagnosed with simultaneous Stanford type A aortic dissection and subsegmental PE, every patient in the early workup group was treated with anticoagulants. Four patients (2.2%) had additional thrombolytic therapy. Median time for start of treatment was 220 min (IQR 155–310 min) in the early, and 4 days (IQR 2–8.3 days) in the delayed workup group. ICU care was not significantly different between the early (22 patients, 12.1%) and delayed (8 patients, 18.2%) workup groups.

The 44 patients with delayed diagnosis were analyzed separately as "early delayed" (14 patients, 31.8%) and "late delayed" (30 patients, 68.2%), showing the following differences in symptom presentation: dyspnea in 10 patients (71.4%), chest pain in 4 patients (28.6%), and nonspecific complaints in 5 patients (35.7%) in the "early delayed" group. In the "late delayed" group, dyspnea was present in 10 patients (33.3%), chest pain in 4 patients (13.3%), and nonspecific complaints in 8 patients (26.7%). Chest CT was used in 10 patients (71.4%) in the "early delayed" and in 14 patients (46.7%) in the "late delayed" subgroups (Table 1).

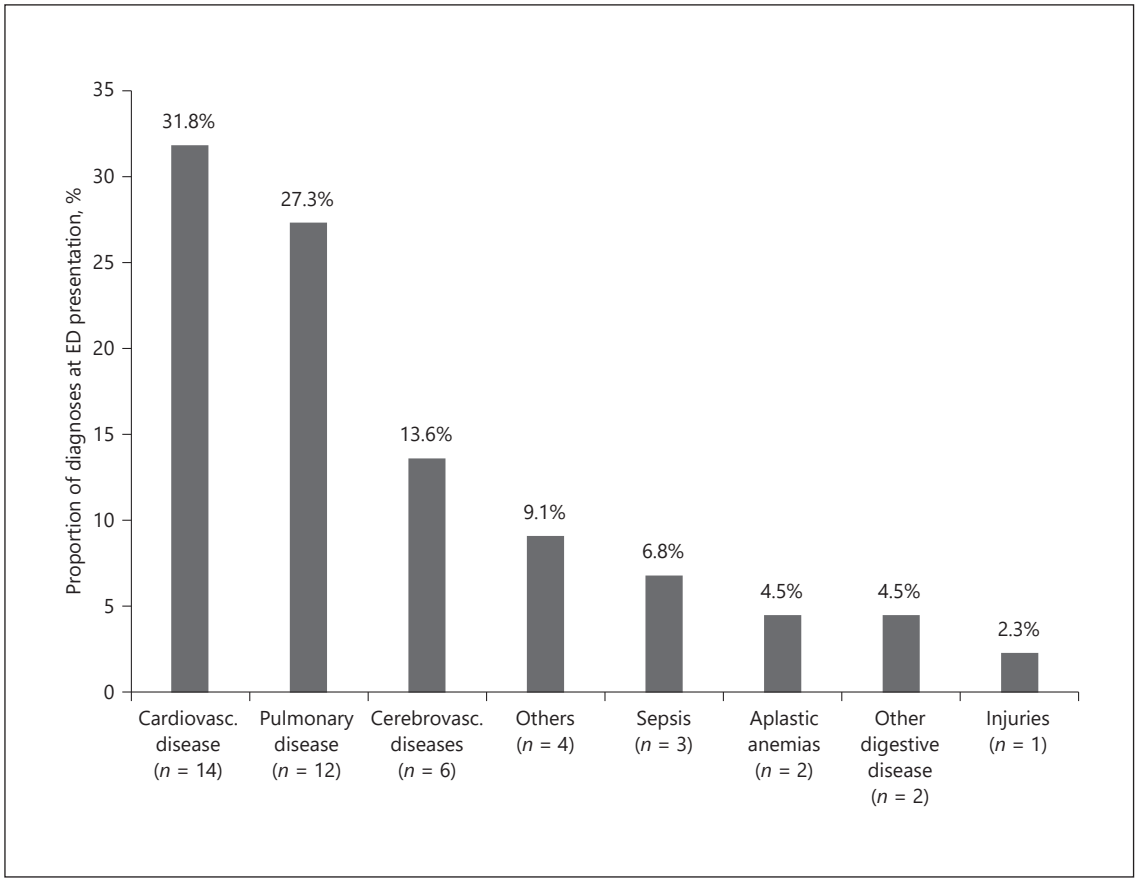

Fig. 2. Initial ED diagnoses in 44 PE patients with delayed workup. Clinical diagnoses according to ICD-10. ICD-10 codes used: cardiovascular disease: I51/I20-I25/R55, pulmonary disease: J18/J44/R06, cerebrovascular diseases: I60–69, sepsis, unspecified organism: A41.9, injury of unspecified body region: T14, other aplastic anemias: D61, other diseases of digestive system: K92, others: K86/R07/R51/D48.

As shown in Figure 2, 14 patients (31.8%) with PE confirmed at delayed workup were initially diagnosed with other cardiovascular disease in the ED, such as cardiomyopathy and heart failure, 12 patients (27.3%) with pulmonary disease, such as pneumonia and exacerbation of chronic obstructive pulmonary disease (COPD), and 6 patients (13.6%) with cerebrovascular disease. As shown in Table 1, 21 (9.3%) of all patients diagnosed with PE had COPD, and there was no significant difference between the early (16 patients, 8.8%) and delayed (5 patients, 11.4%) workup groups.

Among the 937 patients with PE excluded at early workup, 24 patients (2.6%) died. Among the 182 patients with PE confirmed at early workup, 3 patients (1.6%) died, and among the 44 patients with PE confirmed at delayed workup, 19 patients (43.2%) died. Overall, among the 226 patients diagnosed with PE, 22 patients (9.7%) died.

As shown in Table 2, 19 patients underwent autopsy, 3 after radiological diagnosis of PE (patients 1, 4, 5). Of the 16 patients with PE identified only at autopsy (patients 6 to 21), 10 patients had central or paracentral, 5 patients segmental, and 1 patient peripheral PE. Cause of death was acute right ventricular failure (8 patients), respiratory failure/acute pneumonia (7 patients) and myocardial infarction in 1 patient.

Long-Term Follow-Up

Of 204 patients discharged (90.3% of all patients diagnosed with PE), 113 (55.4%) were alive 3 years after the index visit. Of the 179 patients discharged after early diagnosis (98.4% of all patients with early diagnosis of PE), 106 patients (59.2%) were alive 3 years after the index visit. Of the 25 patients discharged after delayed diagnosis (56.8% of all patients with delayed diagnosis of PE), 7 patients (28%) were alive 3 years after the index visit.

Table 2. Causes of mortality

Patient	Age, years	Sex	First clinical diagnosis (ED)	Final clinical diagnosis	Cause of death (autopsy/clinical)	PE location
Early workup						
Patient with autopsy						
1	63	Male	COPD, NSCLC	COPD, PE	Respiratory failure	Segmental
Patients without autopsy						
2	46	Male	PE	PE	Acute right ventricular failure	Central
3	69	Female	PE	PE	Acute right ventricular failure	Paracentral
Delayed workup						
Patients with autopsy						
4	80	Female	Acute heart failure	Acute heart failure, PE	Acute right ventricular failure	Paracentral
5	86	Female	Acute heart failure	PE	Acute right ventricular failure	Central
6	66	Male	Pancreatitis	Pancreatitis	Acute right ventricular failure	Paracentral
7	64	Male	Urosepsis	Urosepsis	Acute right ventricular failure	Paracentral
8	78	Male	Interstitial lung disease	Pneumonia, interstitial	Acute right ventricular failure	Paracentral
9	76	Female	Interstitial lung disease	Right ventricular failure	Acute right ventricular failure	Paracentral
10	77	Female	Stroke	Urosepsis	Acute right ventricular failure	Central
11	62	Male	Abscess, retroperitoneal	Abscess, retroperitoneal	Acute right ventricular failure	Central
12	85	Male	Fall, unknown origin	Myocardial infarction	Acute right ventricular failure	Central
13	88	Female	Myocardial infarction	Myocardial infarction	Acute right ventricular failure	Segmental
14	81	Female	Myocardial infarction	Pneumonia	Respiratory failure	Paracentral
15	82	Male	Stroke	Pneumonia, aspiration	Acute pneumonia	Segmental
16	84	Male	Pneumonia	Pneumonia	Acute pneumonia	Paracentral
17	69	Male	Pneumonia	Pneumonia, aspiration	Acute pneumonia	Segmental
18	83	Male	Pneumonia	Pneumonia	Acute pneumonia	Segmental
19	80	Male	Syncope, renal failure	Renal failure	Acute pneumonia	Peripheral
20	90	Male	Sepsis, unknown origin	Sepsis, unknown origin	Acute pneumonia	Segmental
21	69	Female	Cardiogenic shock	Septic shock	Acute myocardial infarction	Paracentral
Patient without autopsy						
22	51	Male	Pneumonia	Pneumonia, PE	Acute right ventricular failure	Central

Nineteen patients underwent autopsy. In 16 patients, PE was identified only at autopsy (patients 6 to 21), in 3 patients, PE was identified during clinical course and confirmed at autopsy (patients 1, 4, 5). NSCLC, non-small cell lung cancer.

Discussion

The main findings of this study are that delayed diagnoses are common in patients with PE and the patients with delayed diagnosis of PE have a high 30-day mortality rate. Compared to patients with early PE diagnosis, patients with delayed diagnosis were older and had a higher prevalence of nonspecific symptoms at the time of presentation.

There are several potential explanations for a delayed diagnosis in patients with PE. First, patients with a delayed diagnosis were significantly older and had a higher prevalence of nonspecific symptoms at the time of presentation than patients with an early PE diagnosis. Thus, it is not astonishing that two thirds of our patients with delayed diagnoses were initially suspected to have another vascular or pulmonary disease. Evidence suggests that the diagnosis of PE may be more challenging in older patients because the clinical presentation may differ from younger patients. For instance, typical signs and symptoms of PE, such as pleuritic chest pain, hemoptysis, and tachycardia, are less prevalent in older as compared to younger patients with confirmed PE [27]. Indirect evidence that PE is less often suspected in older patients is the low rate of D-dimer testing in patients with a delayed diagnosis in our study. A previous study has suggested that D-dimer testing and the Revised Geneva Score can be used to rule out PE even in patients with delayed clinical presentation [28].

Furthermore, physician factors, including the level of experience, and the inherent stress and time constraints of an ED environment may partly explain diagnostic delays. One might hypothesize that insecurity in decision-making [29] in older patients with nonspecific complaints [10] could contribute to delayed diagnosis. Implicit judgment may be misleading in older patients with a high burden of comorbidity, and clinical diagnostic rules are of little help in patients with an atypical presentation in whom PE is not suspected. As the number of patients undergoing CTPA is rising, the incidence of PE is increasing, most probably due to this increasing scan rate [17, 30] conveying more diag-

noses, but no corresponding increase in mortality. Of note, in-hospital mortality was comparable between patients diagnosed with PE in the ED, in other departments, or in the group excluded per protocol (mostly due to referrals). On the other hand, a strength of the present study is the availability of autopsy data, revealing more delayed PE diagnoses than expected. We might therefore have to reconsider scan rates in older patients, justifying a potentially lower hit rate of PE. However, it is an inherent difficulty that PE detected at autopsy may be questioned as the true cause of mortality. Death due to right ventricular failure was identified in half of all autopsy cases with PE, and embolism was diagnosed only if central or segmental pulmonary artery obstruction was seen. Thus, mortality due to PE was lower than all-cause mortality in the group with delayed diagnoses. Nevertheless, we believe that all missed PE should be accounted for, as even in cases of coexistence of respiratory failure/pneumonia, which accounted for the other half of the mortality, PE cannot be completely excluded as contributing to death.

How does the reported poor outcome in delayed diagnosis compare to the literature? First, the rate of delayed diagnosis is comparable to previous findings (12–32%) [3, 19–23]. However, mortality rates and autopsies were not often reported in previous studies. Therefore, the true incidence of delayed diagnosis could have been underestimated. Mortality in delayed diagnosis of PE was unexpectedly high in our population (43.2%) when compared to the 1.6% in-hospital mortality in early diagnosis. As opposed to delayed diagnosis, a lower PE mortality was reported previously in patients with early diagnosis of PE in the ED [31]. Other comparable studies reported mortality rates ranging from 3 to 20% [17, 32, 33]. Our findings are in line with a study in which PE was found in nearly 20% of patients with otherwise unexplained COPD exacerbation [34]. COPD was also defined as an independent risk factor for PE [35].

Limitations

The major limitation is the retrospective nature of our study, bearing the risk of different types of bias. First, an underestimation of mortality could have occurred as patients discharged from the ED may have been diagnosed in other hospitals or succumbed to sudden death. However, due to billing and health care regulations, and the fact that ours is the only acute care public hospital in the Canton (State), there is a high probability that readmissions should have occurred in the same hospital. Furthermore, PE diagnoses made at other radiology institutions typically lead to referral to our ED (4.3% of all PE), and family physicians also refer to our ED, as outpatient treatment of PE is yet an exception.

Of note, not all patients with a PE diagnosis made at the UHBS are included in the study. All-cause mortality of the 113 patients diagnosed in other departments not admitted through the ED was 11.5%, and that of the 93 patients excluded per protocol was 9.7%.

Second, an overestimation of mortality could have occurred due to the definition that if relevant PE, defined by at least segmental artery occlusion, was found at autopsy, it was defined as PE confirmed at delayed workup. PE can be diagnosed as cause of death or concomitant condition. Therefore, PE-associated mortality in delayed diagnosis due to the inclusion of autopsy data could have been overestimated. Since the immediate cause of death can never be determined without doubt and to prevent underestimation of mortality, we decided to count relevant PE in autopsy as cause of death.

The differential mortality in patients with early versus delayed diagnosis could also be explained by confounding, that is, patients with delayed diagnosis were older and sicker, as indicated by differences in baseline characteristics.

Conclusion

As delayed diagnoses of PE in emergency patients carry a worse prognosis than early diagnoses, every effort should be made for timely workup, particularly in older patients suffering from cardiovascular and chronic pulmonary disease, even if presenting with nonspecific complaints.

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Statement of Ethics

The study protocol was approved by the local Ethics Committee; informed consent was waived due to sample size and the retrospective nature of the study (EKNZ 2014-183). This study is reported according to the STROBE guidelines, is in accordance with the Declaration of Helsinki, and is registered at www.clinicaltrials.gov, NCT02476721.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

G.M. detailed chart reviews, data analysis, and writing of the manuscript. C.K. study design, data acquisition, and writing of the manuscript. C.H.N. study design, critical revision of the manuscript for important intellectual content. C.E. critical revision of the manuscript and statistical expertise. C.W. analysis of the data. A.T. revision of autopsy records. C.J.P. data acquisition. D.A. critical revision of the manuscript. R.B. study supervisor and sponsor investigator, study design, critical revision of the manuscript.

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