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Clinical characteristics associated with diagnostic delay of pulmonary embolism in primary care: a retrospective observational study.

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ABSTRACT

Objectives: To evaluate the extent of delay in the diagnosis of pulmonary embolism (PE) in primary care, and to identify determinants that are associated with such diagnostic delay.

Design: Retrospective observational study.

Setting: Six primary care practices across The Netherlands.

Participants: Patients with an objectively confirmed diagnosis of pulmonary embolism (ICPC-code K93) up to June 2015 were extracted from the electronic medical records. For all these PE events we reviewed all consultations with their general practitioner (GP) and scored any signs and symptoms that could be attributed to PE in the 3 months prior to the event. Also, we documented actual comorbidity and the diagnosis considered initially.

Primary and secondary outcome measures: Delay was defined as a time gap of >7 days between the first contact with the GP and the final diagnosis. Multivariable logistic regression analysis was performed to identify independent determinants for delay.

Results: In total 180 incident PE cases were identified, of whom 128 patients had one or more potential PE-related contact with their GP within the three months prior to the diagnosis. Based on our definition, in 33 of these patients (26%) diagnostic delay was observed. Older age (age >75 years) (OR 5.10 (95%CI 1.84-14.13)) and the absence of chest complaints (that is: chest pain or pain on inspiration) (OR 5.37 (95%CI 1.90-15.16)) were independent determinants for diagnostic delay. A respiratory tract infection prior to the PE diagnosis was reported in 14% of all cases, and in 33% of patients with delay.

Conclusions: Diagnostic delay of more than seven days in the diagnosis of pulmonary embolism is common in primary care, especially in elderly and if chest complains, like pain on inspiration, are absent.

Strengths and limitations of this study

* This study identified objectively confirmed cases of pulmonary embolism (PE) based on ICPC-coding in Dutch primary care practices. In all PE cases, individual patient files were reviewed by at least two researchers independently to identify potential diagnostic delay.

* Using the electronic individual patient files, we were able to assess not only information on GP consultations, but also correspondence between GPs, hospital specialists and results from laboratory and imaging tests performed.

* Since we had to rely on correct ICPC-coding in all primary care practices, there is a chance of incomplete selection of all PE cases. However, we believe that this miscoding will be present in only a minor fraction of all PE cases given the relevance of correct coding.

*Furthermore, our study is limited by not including information on determinants like oxygen saturation, heart rate and D-dimer levels due to incomplete recordings.

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

INTRODUCTION

Pulmonary embolism (PE) is listed among the diagnoses most frequently missed, or delayed, in clinical practice. (1) In fact, a substantial part of the estimated 500,000 deaths per year attributed to venous thromboembolism in Europe is likely to be contributed to a missed or delayed diagnosis. (2) This delay is thought to be driven primarily by a non-specific disease presentation. The classical triad of dyspnoea, pain on inspiration and haemoptysis is only present in 10% of the patients with PE. (3) Instead, PE presentation can range from complaints mimicking a simple cough or myalgia, an acute myocardial infarction or even nephrolithiasis. This non-specific presentation poses a major diagnostic challenge to physicians to identify PE timely. Prompt recognition of the diagnosis, and consequent immediate initiation of anticoagulant therapy, is important to prevent severe complications and mortality, and is recommended by current guidelines. (4, 5)

The evidence on appropriate strategies to diagnose PE is overwhelming, yet all these strategies by definition start with a suspicion of PE. In contrast, limited evidence is available on the magnitude of delayed PE diagnoses and determinants associated with such diagnostic delay. The current evidence comes largely from studies performed in emergency departments (EDs). These studies identified that diagnostic delay was common, yet with varying proportion of delayed PE cases (range 12% to 75% of PE cases). (6-13) Furthermore, the definitions used to quantify delay were heterogeneous. Various determinants like higher age, comorbidity (e.g. chronic obstructive pulmonary disease (COPD), cardiovascular disease), absence of dyspnoea and no pain on respiration were associated with a delay in diagnosis, but these findings were not consistent across studies.

In many countries general practitioners (GPs) fulfil a pivotal gate-keeping role for access to subsequent hospital care. Yet, GPs have only limited diagnostic tools available on the spot and often have to rely substantially on clinical assessment. Appreciating the relatively high reported number of PE events missed or delayed in a pre-selected ED population and the diagnostic limitations in primary care, we hypothesize that delay is likely to be present frequently in primary care as well. However, only one recent publication reports on both patient and primary care delay, and on delay-related determinants. (14) More evidence on the extent of delay and knowledge on determinants might help GPs to better identify patients with PE in time.

Therefore, the two aims of the present study were to explore the extent of diagnostic delay in primary care, and to identify determinants that are associated with this diagnostic delay.

METHODS

Study design

We performed an observational study in six primary care practices in the Netherlands. The study was assessed by the local Institutional Ethics Review Board and received a waiver for formal reviewing. As such, according to Dutch law, no explicit informed consent was required as data reducible to the patients was only available at the GPs practices and made anonymous for data evaluation and analysis by the researchers.

Study population

All patient contacts labelled with the International Classification of Primary Care (ICPC)-code K93 (i.e. diagnosis of pulmonary embolism) until June 2015 were extracted from the electronic patient records (EPR) of the six practices. Next, detailed information on all consultations three months prior to the PE diagnosis were scrutinized using the following approach. First, all patients with an ICPC-code K93 were validated on the actual presence of PE by the researchers (MM, MvR) using hospital discharge information, including results from imaging and medication prescriptions. In case of doubt another reviewer was consulted (JH, GJG). Patients were excluded from further analysis if PE was considered absent, if insufficient information on the PE event was available to confirm the diagnosis, if no objective imaging was performed (e.g. in palliative patients) or if the ICPC-code was assigned incorrectly in the EPR (e.g. if PE was suspected initially, but ruled out after referral and objective imaging). Additionally, the diagnosis PE was confirmed if anticoagulant therapy was initiated post-event and if the hospital discharge letter described the presence of PE based on diagnostic imaging tests.

Outcome: diagnostic delay

We assessed all GP contacts prior to the final diagnosis PE on their relevance in relation to the final PE diagnosis. Patient contacts were considered to be relevant for this PE event when the patient had presented with any of the following signs or symptoms: dyspnoea, cough, haemoptysis, chest pain, painful respiration, fever (body temperature >38^{o}C), increased respiratory rate, increased heart rate, low oxygen saturation, or signs of deep venous thrombosis (DVT). If data on these items were not reported, we considered them absent. In all other cases (e.g. regular diabetes work-up, psychosocial problems) we tagged these contacts as not diagnostically relevant to the final PE diagnosis. Additionally, the initial diagnosis suspected by

the GP at the time of the first patient contact, relevant for the final PE event, was registered in all cases. Also the number of days between the first presentation of any of our pre-defined signs or symptoms relevant for PE at the GP and the final PE diagnosis was calculated. Cases in which there was any doubt regarding relevance of GP contacts were discussed during consensus meetings (MM, MvR, JH and GJG).

The outcome, delay in PE diagnosis, was defined as a period longer than 7 days between the patient's first GP contact attributed to be relevant for PE (based on our aforementioned definition) and the final PE diagnosis, similar to a previous study on diagnostic delay. (10) Immediate referral to the emergency department based on the suspicion of another condition than PE was not considered to be delay, since the severity of the condition was acknowledged.

Potential determinants of diagnostic delay

The following determinants were assessed to be a potential determinant for diagnostic delay: older age (>75 years), gender, risk factors for PE (i.e. recent immobilization, prior venous thromboembolism, systemic oestrogen use, pregnancy, puerperium and recent surgery), medical history (i.e. COPD, asthma, hypertension, coronary artery disease, heart failure, atrial fibrillation, (past) smoking and malignancy (based on ICPC coding and/ or referral letters as recorded in the EPR)). Finally, results of D-dimer testing were assessed.

Statistical analyses

The determinants were first compared between patients with and without a delay in diagnosis in a univariable analysis. Continuous variables were presented as mean (standard deviation (SD)) or median (interquartile range (IQR)) and compared with the independent sample T-test or the

Mann-Whitney U test. Categorical variables were reported as the absolute number (plus percentage) and compared using the Chi-square test or Fisher's Exact test.

We then performed multivariable logistic regression analysis using presence or absence of diagnostic delay as the binary outcome to assess which of the potential determinants were independently associated with delayed PE diagnosis. First, we constructed a logistic model using signs and symptoms, age and gender as potential determinants for diagnostic delay. Next, this logistic model was extended with co-morbidity in a second model, to gain further insight into the type of patients in whom a delay of diagnosis occurs more often in primary care medicine. Regression coefficients from the logistic models were recalculated into odds ratios with their surrounding 95% confidence interval.

Given the exploratory nature of this study as well as the uncertainty around the scope of diagnostic delay for PE in primary care we deliberately chose not to define statistical criteria regarding sample size. Instead, acknowledging the fact that our study sample would not allow for a selection of variables into the logistic models based on p-values, we a priori defined the variables that we wanted to assess in the logistic models. This variable selection was entirely based upon previous literature review, and included gender, age, absence of chest complaints (i.e. pain on inspiration and chest pain), and the absence of dyspnoea for the first logistic model, and additionally a prior respiratory chest infection and asthma/COPD for the second logistic model. Data were analysed using SPSS 21.0 (SPSS Inc, Chicago, IL).

RESULTS

Approximately 50,400 patients were registered in the six general practices that participated. Using the ICPC-code K93, 251 possible pulmonary embolism cases were identified until June 2015. Seventy-one cases were excluded based on the predefined exclusion criteria. For the majority of cases (n=54) no detailed information was available, for example if the event took place years ago while registered in another practice. In total, 180 verified PE cases were left for further analyses (see *Figure 1*). Forty-nine patients (27%) had no contact with their GP prior to the PE event and in three (palliative care) patients no objective imaging was performed. See *Table 1* for further characteristics of the group of patients that did not contact their GP in the period prior to the PE diagnosis. This latter group included more patients with a recent surgery, active malignant disease, but less patients with cardiac or respiratory comorbidities. The remaining 128 patients had relevant contact moments with their GP prior to the diagnosis and were included in our main analysis. In 33 of these patients (26%), diagnostic delay as defined a-priori was observed.

Patients with a delay in diagnosis were on average older, had less frequent chest pain (24% vs. 54%, p = 0.003) and less frequent pain on respiration (9% vs. 33%, p= 0.011) on initial presentation. Diagnosis was more often delayed in patients with a recent respiratory tract infection (33% vs. 13%, p= 0.008) (see *Table 2*). In the first multivariable logistic regression analysis, older age (OR 5.10 (95%CI 1.84-14.13)) and the absence of chest complaints (OR 5.37 (95%CI 1.90-15.16)) were associated with diagnostic delay (see *Table 3a*). In the second model, female gender, absence of dyspnoea and prior respiratory tract infections were associated with delay in diagnosis too (see *Table 3b*).

DISCUSSION

In this study on the extent of diagnostic delay of pulmonary embolism in primary care and its determinants, we observed that diagnostic delay was present in a substantial proportion of patients (26%). An important factor associated with diagnostic delay appeared to be the absence of the typical "text book" chest pain symptoms as presented during the first presentation at the general practitioner. Furthermore, in those with diagnostic delay, a respiratory tract infection was frequently reported, before the initial PE diagnosis was established.

This is one of the first studies on the magnitude of diagnostic delay of pulmonary embolism in a primary care setting. Strength of this study is the fact that we had access to the general practitioner's electronic patients records, including all consultations with the GP prior to the diagnosis, plus the correspondence between GPs and hospital specialists and all results from laboratory and imaging tests performed. This allowed us to sketch a complete and detailed picture of the diagnostic pathway starting from the first presentation of patients with signs and symptoms at their GP to the final diagnosis of PE.

However, for full appreciation of these results, some limitations need to be addressed. Foremost, we used a retrospective design to quantify diagnostic delay, which incurs several challenges.

First, we had to rely on correct ICPC-coding in all primary care practices. Only cases with the ICPC-code K93 were extracted for detailed assessment, leaving the chance of erroneously leaving out PE cases that were labelled with an incorrect ICPC-code. This could be the case if a patient is referred to secondary care with non-specific complaints like dyspnoea, consequently

coded as such, without updating of the coding to PE afterwards. We however believe that this miscoding will be present only in a fraction of all PE cases, given that PE is an important diagnosis to be reported for further anticoagulant use and because of its prognostic implications. Another reason for incomplete selection of PE cases is the fact that patient records of those deceased were not available for all. This leaves the chance of missing PE events in patients that occurred in the years prior to their passing.

Second, data on determinants like oxygen saturation, heart rate and D-dimer levels were not reported in the patient records of many cases. For the current analyses, we assumed that the variable was not present if information on that item was not reported. However, it cannot be said for sure if these variables were not measured at all, or absent if not reported. Especially if PE is not suspected by the GP, it can be expected that not all PE risk factors and signs (e.g. recent traveling or respiratory rate) are explicitly asked. If so, this can lead to selective underreporting of specific determinants. In an attempt to gain insight into the possible selective reporting, we performed a sensitivity analysis in which we tested for the distribution of non-reported factors between the patients with and without delay. No differences were observed, however (data not shown).

Third, we had to make interpretations on the relevance of certain complaints for the diagnosis PE, all with current knowledge that PE was indeed present. Since blinding is not possible in a retrospective design, no measures could be taken to prevent this.

Nevertheless, being aware of all these drawbacks of using a retrospective study design, we deemed this design to be the most suitable method to study delay in diagnosis. By definition, delay is only to be determined with hindsight and as a consequence, prospective evaluation of the diagnostic process will be difficult for a disease with a relatively low incidence in primary care.

We arbitrarily defined diagnostic delay as a time lag of >7 days between the first presentation at the GP and the final diagnosis. However, a lag period of >7 seven days can be deemed to be too large, especially considering the potential fatal outcome of not treating a PE event in time. (5) Therefore, we performed a sensitivity analysis in which we set the definition of diagnostic delay at 1 or more GP contact without adequate referral to secondary care for further diagnostics. Using this (more stringent) definition of diagnostic delay, the proportion of cases missed increased to over 40% (data not shown). Yet, the inferences on our reported determinants of delay remained constant, strengthening the validity of our findings.

Another complicating factor in the definition of delay in PE diagnosis concerns its physiological development and progression. In recent years, much has been written on the interplay of inflammation and an activated thrombogenic state. (15, 16) Thus, an infection could also be the precursor of, and provoking factor for, PE. An initial diagnosis of a respiratory tract infection that turns out to be a PE a few days later is not necessarily a delayed PE diagnosis. Instead, the PE can rather be the result of a cascade initiated by the infection. This distinction between a PE initiated by an infection, and a PE incorrectly diagnosed as an infection, cannot be made easily, leaving the chance of overestimation of the association between diagnostic delay and a respiratory tract infection. This possible interplay between infection and venous thrombosis was also observed the other way around in a recent study by Timp and colleagues. (17) Patients receiving antibiotics (as a proxy for infectious disease) had an increased risk of both first and recurrent VTE (incidence rate ratio (IRR) 5.6 (95% CI 4.6-6.8)). Analogue to our inferences, this point estimate may have been too high due to misclassification of PE symptoms

as an infection, and thus inappropriate prescription of antibiotics. The latter in fact would be classified as delay in diagnosis in our study.

In seven PE cases without diagnostic delay, the diagnosis of PE was not considered initially by the GP. However, due to the suspicion of another serious condition (acute coronary event), urgent referral to the emergency department led to prompt diagnosis of PE anyhow. In the strict sense of the definition, the diagnosis PE is missed here since it was not the diagnosis deemed to be most likely by the GP. We treated these missed, but adequately referred, cases as "delay present" in a sensitivity analysis, not changing our inferences (data not shown).

Finally, we did not collect data on the clinical implications of diagnostic delay, like quality of life or long-term health effects. However, knowledge on the impact of delay on clinical outcomes is important to be able to value the relevance of delayed diagnoses: it can be hypothesized that long-term outcomes are worse for patients who have had a prolonged duration of complaints, caused by the lengthened exposure to vessel obstruction, and consequent vessel damage, pulmonary hypertension or lung infarction. Further prospective research however is needed to address this research question for the primary care domain.

Comparison with other studies

A few studies on delay in diagnosis of pulmonary embolism have been performed in secondary care, especially in emergency departments. For example, Torres-Macho et al. found that patients with diagnostic delay in an emergency department were older, had more frequently COPD or asthma, and presented more often with a cough, fever and tachycardia. (8) In the study by Alonso- Martinez and colleagues, delay was also more prevalent amongst elderly, and in those with previous cardiac disease and without sudden onset of dyspnoea. (6) In our study, older age

was associated with diagnostic delay too, just like the absence of typical PE complaints. However, female gender was not reported previously in relation with delay. Only one study mentioned female gender as a risk factor for patient-delay rather than doctor-delay. (13) Given our small sample size and exploratory nature, these findings require further evaluation in future research. A recent retrospective study was conducted in a Dutch secondary care setting in which delay in primary care was estimated as well. Whereas 75% of patients were referred within one day, the remaining 25% had an average delay of 15.7 days. One important determinant for early referral was the presence of chest pain. This is in line with our results, in which the absence of chest symptoms was associated with diagnostic delay.

Clinical implications

Given the substantial percentage of cases with delay in diagnosis of PE observed in this current study, we assume that most GPs come across a situation with diagnostic delay in PE regularly. Even if an alternative diagnosis is confirmed (e.g. infiltrate on chest radiography, or an initial improvement after the initiation of antibiotic treatment), PE can be present simultaneously, or develop along the course of the concurrent disease. Therefore, we argue that an initial diagnosis should be reconsidered frequently, especially if symptoms do not improve as much as can be expected, and in those with coexisting cardiopulmonary conditions.

Furthermore, we showed in this current study that the diagnosis of PE is more often delayed in case of non-typical presentation of complaints. Therefore, we suggest GPs to consider PE as a potential diagnosis even if symptoms are not overwhelmingly pointing into that direction. To prevent an overshoot of referrals to secondary care as a consequence of this low threshold of suspicion, a diagnostic prediction model might help GPs to further guide the

decision whether or not to refer a patient. (18) Nevertheless, especially in elderly and those with concurrent respiratory tract infections, the false-positive rate of these prediction models (specifically the D-dimer test) is considerable. (19, 20) As such, the optimal balance between raised awareness of PE and refraining from over-referral has yet to be found and further evaluation of diagnostic delay is needed.

CONCLUSION

Diagnostic delay of pulmonary embolism is common in primary care, especially if classical PE symptoms like chest complaints are absent. Awareness of the possibility of a PE being the underlying cause of a wide range of symptoms, might contribute to a reduction of the number of delayed PE diagnoses in primary care.

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Author's contribution

Conception and design of the work (JH, GJG, KM), data collection (JH, MK-vR, MM, GJG), data analysis and interpretation (JH, MK-vR, MM, GJG, KM), drafting the article (JH, MK-vR, MM, GJG), critical revision of the article (RS, RO, KM), final approval of the version to be published (JH, MK-vR, MM, RO, RS, KM, GJG)

Data sharing statement

The dataset and statistical codes are available from the authors upon request.

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Table 1- Characteristics of patients with and without GP visit before diagnosis PE

	No prior GP visit (n=49)	**Prior GP contact(s)** (n=128)	**p-value**
Age in years***, mean (± SD)	60 (17)	58 (16)	0.429
Male gender	27 (55)	60 (47)	0.327
Comorbidity			
COPD/ asthma	5 (10)	27 (21)	0.067*
Hypertension	11 (22)	37 (29)	0.387
Atrial fibrillation	1 (2)	4 (3)	1.000*
Congestive heart failure	0 (0)	6 (5)	0.189*
Ischemic heart disease	3 (6)	14 (11)	0.406*
Risk factors			
History of DVT	7 (14)	26 (20)	0.357
Recent surgery	8 (16)	8 (6)	0.045*
Recent immobilization	4 (8)	6 (5)	0.467*
Recent travelling	2 (4)	4 (3)	0.669*
Malignancy	9 (18)	10 (8)	0.042
Estrogen use, women	0/22 (0)	19/68 (28)	0.005*
Prior pulmonary infection	3 (6)	23 (18)	0.057*
History of smoking	6 (12)	33 (26)	0.052
Pregnancy	0/22 (0)	3/68 (4)	1.000
Days until diagnosis, median [IQR]	0 [0]	1 [8]	
total range	NA	0-126 days	
Delay > 7 days	NA	33 (26)	

Values are numbers (percentages) unless stated otherwise. *Fisher's exact test *** missing values (n=3)
PE= pulmonary embolism; GP= general practitioner; SD= standard deviation; COPD= chronic obstructive pulmonary disease; DVT= deep venous thrombosis; IQR= interquartile range; NA= not applicable.

Table 2- Baseline characteristics *(diagnostic delay >7 days)*

	No diagnostic delay (n=95)	**Diagnostic delay > 7 days** (n=33)	**p-value**
Age in years*, mean (± SD)	56 (15)	62 (18)	0.068
Male gender	47 (49)	13 (39)	0.317
Symptoms			
Dyspnea	62 (65)	22 (67)	0.884
Chest complaints	59 (62)	9 (27)	0.001
Chest pain	51 (54)	8 (24)	0.003
Painful respiration	31 (33)	3 (9)	0.011*
Cough	17 (18)	12 (36)	0.029
Hemoptysis	3 (3)	1 (3)	1.000*
Signs of DVT	18 (19)	1 (3)	0.025*
Fever (>38°C)	5 (5)	2 (6)	1.000*
Collapse	4 (4)	0 (0)	0.572*
Heart rate, mean (± SD)	96 (19)	95 (26)	0.916
O_2 saturation, median [IQR]	96 [5]	94 [9]	0.124
Comorbidities			
COPD and/or asthma	14 (15)	13 (39)	0.004
Hypertension	25 (26)	12 (36)	0.273
Atrial fibrillation	2 (2)	2 (6)	0.273*
Congestive heart failure	3 (3)	3 (9)	0.177*
Ischemic heart disease	10 (11)	4 (12)	0.755*
Risk factors			
History of DVT	18 (19)	8 (24)	0.515
Recent surgery	7 (7)	1 (3)	0.679*
Recent immobilization	6 (6)	0 (0)	0.338*
Recent travelling	4 (4)	0 (0)	0.572*
Malignancy	7 (7)	3 (9)	0.717*
Estrogen use, women	15/48 (31)	4/20 (20)	0.393*
Prior pulmonary infection	12 (13)	11 (33)	0.008
History of smoking	26 (27)	7 (21)	0.486
Pregnancy	3/48 (6)	0/20 (0)	0.550

Values are numbers (percentages) unless stated otherwise. *Fisher's exact test *** missing values (n=3)
PE= pulmonary embolism; SD= standard deviation; DVT= deep venous thrombosis; IQR= interquartile range; COPD= chronic obstructive pulmonary disease; NA= not applicable.

Table 3a- Multivariable regression model for the association between signs and symptoms with a diagnostic delay > 7 days

MODEL 1	OR (95%CI)	p-value
Female gender	2.47 (0.93-6.61)	0.071
Age >75	5.10 (1.84-14.13)	0.002
No chest complaints	5.37 (1.90-15.16)	0.002
No dyspnea	2.29 (0.81-6.46)	0.118

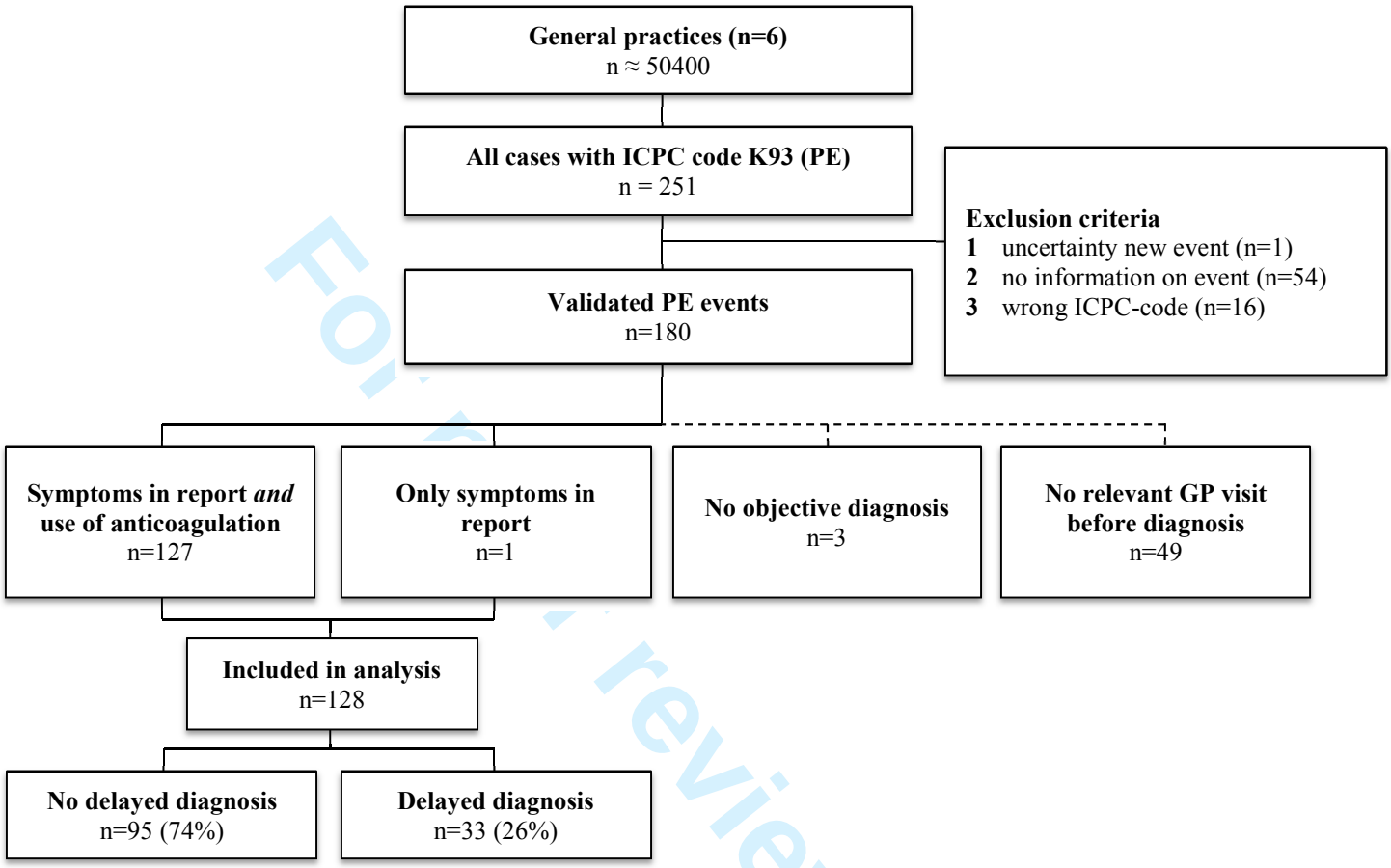
OR= odds ratio; 95%CI= 95% confidence interval.

Table 3b- Multivariable logistic regression model for the association between signs, symptoms and comorbidity with a diagnostic delay >7 days

MODEL 2	OR (95%CI)	p-value
Female gender	3.08 (1.08-8.78)	0.036
Age >75	4.28 (1.49-12.28)	0.007
No chest complaints	5.35 (1.79-16.05)	0.003
No dyspnea	3.08 (1.01-9.35)	0.047
Prior respiratory tract infection	3.34 (1.11-10.01)	0.031
COPD/asthma	3.34 (0.88-7.54)	0.085

OR= odds ratio; 95%CI= 95% confidence interval.

Figure 1- Flow chart of the selection of pulmonary embolism cases in primary care



PE= pulmonary embolism; ICPC= international classification of primary care; GP= general practitioner

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Clinical characteristics associated with diagnostic delay of pulmonary embolism in primary care: a retrospective observational study.

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ABSTRACT

Objectives: To evaluate the extent of delay in the diagnosis of pulmonary embolism (PE) in primary care, and to identify determinants that are associated with such diagnostic delay.

Design: Retrospective observational study.

Setting: Six primary care practices across The Netherlands.

Participants: Patients with an objectively confirmed diagnosis of pulmonary embolism (ICPC-code K93) up to June 2015 were extracted from the electronic medical records. For all these PE events we reviewed all consultations with their general practitioner (GP) and scored any signs and symptoms that could be attributed to PE in the 3 months prior to the event. Also, we documented actual comorbidity and the diagnosis considered initially.

Primary and secondary outcome measures: Delay was defined as a time gap of >7 days between the first potentially PE-related contact with the GP and the final PE diagnosis. Multivariable logistic regression analysis was performed to identify independent determinants for delay.

Results: In total 180 incident PE cases were identified, of whom 128 patients had one or more potential PE-related contact with their GP within the three months prior to the diagnosis. Based on our definition, in 33 of these patients (26%) diagnostic delay was observed. Older age (age >75 years) (OR 5.1 (95%CI 1.8-14.1)) and the absence of chest complaints (that is: chest pain or pain on inspiration) (OR 5.4 (95%CI 1.9-15.2)) were independent determinants for diagnostic delay. A respiratory tract infection prior to the PE diagnosis was reported in 13% of cases without delay, and in 33% of patients with delay (p=0.008).

Conclusions: Diagnostic delay of more than seven days in the diagnosis of pulmonary embolism is common in primary care, especially in elderly and if chest complains, like pain on inspiration, are absent.

Strengths and limitations of this study

* This study identified objectively confirmed cases of pulmonary embolism (PE) based on ICPC-coding in Dutch primary care practices. In all PE cases, individual patient files were reviewed by at least two researchers independently to identify potential diagnostic delay.

* Using the electronic individual patient files, we were able to assess not only information on GP consultations, but also correspondence between GPs, hospital specialists and results from laboratory and imaging tests performed.

* Since we had to rely on correct ICPC-coding in all primary care practices, there is a chance of incomplete selection of all PE cases. However, we believe that this miscoding will be present in only a minor fraction of all PE cases given the relevance of correct coding.

*Furthermore, our study is limited by not including information on determinants like oxygen saturation, heart rate and D-dimer levels due to incomplete recordings.

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Competing interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in

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INTRODUCTION

Pulmonary embolism (PE) is listed among the diagnoses most frequently missed, or delayed, in clinical practice. (1) In fact, a substantial part of the estimated 500,000 deaths per year attributed to venous thromboembolism in Europe is likely to be contributed to by a missed or delayed diagnosis. (2) This delay is thought to be driven primarily by a non-specific disease presentation. The classical triad of dyspnoea, pain on inspiration and haemoptysis is only present in 10% of the patients with PE. (3) Instead, PE presentation can range from complaints mimicking a simple cough or myalgia, an acute myocardial infarction or even nephrolithiasis. This non-specific presentation poses a major diagnostic challenge to physicians to identify PE timely. Prompt recognition of the diagnosis, and consequent immediate initiation of anticoagulant therapy, is important to prevent severe complications and mortality, and is recommended by current guidelines. (4, 5)

The evidence on appropriate strategies to diagnose PE is overwhelming, yet all these strategies by definition start with a suspicion of PE. In contrast, limited evidence is available on the magnitude of delayed PE diagnoses and determinants associated with such diagnostic delay. The current evidence comes largely from studies performed in emergency departments (EDs). These studies identified that diagnostic delay was common, yet with varying proportion of delayed PE cases (range 12% to 75% of PE cases). (6-13) Furthermore, the definitions used to quantify delay were heterogeneous. Various determinants like higher age, comorbidity (e.g. chronic obstructive pulmonary disease (COPD), cardiovascular disease), absence of dyspnoea and no pain on respiration were associated with a delay in diagnosis, but these findings were not consistent across studies.

In many countries general practitioners (GPs) fulfil a pivotal gate-keeping role for access to subsequent hospital care. Yet, GPs have only limited diagnostic tools available on the spot and often have to rely substantially on clinical assessment. Appreciating the relatively high reported number of PE events missed or delayed in a pre-selected ED population and the diagnostic limitations in primary care, we hypothesize that delay is likely to be present frequently in primary care as well. However, only one recent publication reports on both patient and primary care delay, and on delay-related determinants like comorbidity and the absence of chest pain. (14) More evidence on the extent of delay and knowledge on determinants might help GPs to better identify patients with PE in time.

Therefore, the two aims of the present study were to explore the extent of diagnostic delay in primary care, and to identify determinants that are associated with this diagnostic delay.

METHODS

Study design

We performed an observational study in six primary care practices in the Netherlands. The study was assessed by the local Institutional Ethics Review Board and received a waiver for formal reviewing. As such, according to Dutch law, no explicit informed consent was required as data reducible to the patients was only available at the GPs practices and made anonymous for data evaluation and analysis by the researchers.

Study population

All patient contacts labelled with the International Classification of Primary Care (ICPC)-code K93 (i.e. diagnosis of pulmonary embolism) were extracted from the electronic patient records (EPR) of the six practices. Next, detailed information on all consultations three months prior to the PE diagnosis were scrutinized using the following approach. First, all patients with an ICPC-code K93 were validated on the actual presence of PE by the researchers (MM, MvR) using hospital discharge information, including results from imaging and medication prescriptions. In case of doubt another reviewer was consulted (JH, GJG). Patients were excluded from further analysis if PE was considered absent, if insufficient information on the PE event was available to confirm the diagnosis, if no objective imaging was performed (e.g. in palliative patients) or if the ICPC-code was assigned incorrectly in the EPR (e.g. if PE was suspected initially, but ruled out after referral and objective imaging). Additionally, the diagnosis PE was confirmed if anticoagulant therapy was initiated post-event and if the hospital discharge letter described the presence of PE based on diagnostic imaging tests.

Outcome: diagnostic delay

We assessed all GP contacts prior to the final diagnosis PE on their relevance in relation to the final PE diagnosis. Patient contacts were considered to be relevant for this PE event when the patient had presented with any of the following signs or symptoms: dyspnoea, cough, haemoptysis, chest pain, painful respiration, fever (body temperature >38^{o}C), increased respiratory rate, increased heart rate, low oxygen saturation, or signs of deep venous thrombosis (DVT). If data on these items were not reported, we considered them absent. In all other cases (e.g. regular diabetes work-up, psychosocial problems) we tagged these contacts as not

diagnostically relevant to the final PE diagnosis. Additionally, the initial diagnosis suspected by the GP at the time of the first patient contact, relevant for the final PE event, was registered in all cases. Also the number of days between the first presentation of any of our pre-defined signs or symptoms relevant for PE at the GP and the final PE diagnosis was calculated. Cases in which there was any doubt regarding relevance of GP contacts were discussed during consensus meetings (MM, MvR, JH and GJG).

The outcome, delay in PE diagnosis, was defined as a period longer than 7 days between the patient's first GP contact attributed to be relevant for PE (based on our aforementioned definition) and the final PE diagnosis, similar to a previous study on diagnostic delay. (10) Immediate referral to the emergency department based on the suspicion of another condition than PE was not considered to be delay, since the severity of the condition was acknowledged.

Potential determinants of diagnostic delay

The following determinants were assessed to be a potential determinant for diagnostic delay: older age (post-hoc chosen cut-off >75 years, given the assumption that symptoms are often less specific at higher age), gender, risk factors for PE (i.e. recent immobilization, prior venous thromboembolism, systemic oestrogen use, pregnancy, puerperium and recent surgery), medical history (i.e. COPD, asthma, hypertension, coronary artery disease, heart failure, atrial fibrillation, (past) smoking and malignancy (based on ICPC coding and/ or referral letters as recorded in the EPR)).

Statistical analyses

The determinants were first compared between patients with and without a delay in diagnosis in a univariable analysis. Continuous variables were presented as mean (standard deviation (SD)) or median (interquartile range (IQR)) and compared with the independent sample T-test or the Mann-Whitney U test. Categorical variables were reported as the absolute number (plus percentage) and compared using the Chi-square test or Fisher's Exact test.

We then performed multivariable logistic regression analysis using presence or absence of diagnostic delay as the binary outcome to assess which of the potential determinants were independently associated with delayed PE diagnosis. First, we constructed a logistic model using signs and symptoms, age and gender as potential determinants for diagnostic delay. Next, this logistic model was extended with co-morbidity in a second model, to gain further insight into the type of patients in whom a delay of diagnosis occurs more often in primary care medicine. Regression coefficients from the logistic models were recalculated into odds ratios with their surrounding 95% confidence interval.

Given the exploratory nature of this study as well as the uncertainty around the scope of diagnostic delay for PE in primary care we deliberately chose not to define statistical criteria regarding sample size. Instead, acknowledging the fact that our study sample would not allow for a selection of variables into the logistic models based on p-values, we a priori defined the variables that we wanted to assess in the logistic models. This variable selection was entirely based upon previous literature review, and included gender, age, absence of chest complaints (i.e. pain on inspiration and chest pain), and the absence of dyspnoea for the first logistic model, and additionally a prior respiratory chest infection and asthma/COPD for the second logistic model. It should be noted that there is a potential risk of overfitting when including too many variables into a logistic models in respect to the number of delayed cases. Therefore, the second

model is regarded to be only an extension to the first model to explore the influence of knowledge on comorbidity and should be interpreted as such. Data were analysed using SPSS 21.0 (SPSS Inc, Chicago, IL).

RESULTS

Approximately 50,400 patients were registered in the six general practices that participated. Using the ICPC-code K93, 251 possible pulmonary embolism cases were identified, with varying starting dates per practice due to logistics reasons (first PE event 1994) until June 2015. Seventy-one cases were excluded based on the predefined exclusion criteria. For the majority of cases (n=54) no detailed information was available, for example if the event took place years ago while registered in another practice. In total, 180 verified PE cases were left for further analyses (see *Figure 1*). Forty-nine patients (27%) had no contact with their GP prior to the PE event and in three (palliative care) patients no objective imaging was performed. See *Table 1* for further characteristics of the group of patients that did not contact their GP in the period prior to the PE diagnosis. This latter group included more patients with a recent surgery, active malignant disease, but less patients with cardiac or respiratory comorbidities. The remaining 128 patients had relevant contact moments with their GP prior to the diagnosis and were included in our main analysis. In 33 of these patients (26%), diagnostic delay as defined a-priori was observed.

Patients with a delay in diagnosis were on average older, had less frequent chest pain (24% vs. 54%, p = 0.003) and less frequent pain on respiration (9% vs. 33%, p= 0.011) on initial presentation. Diagnosis was more often delayed in patients with a recent respiratory tract

infection (33% vs. 13%, p= 0.008) (see *Table 2*). In the first multivariable logistic regression analysis, older age (OR 5.1 (95%CI 1.8-14.1)) and the absence of chest complaints (OR 5.4 (95%CI 1.9-15.2)) were associated with diagnostic delay (see *Table 3a*). In the second model, female gender, absence of dyspnoea and prior respiratory tract infections were associated with delay in diagnosis too (see *Table 3b*).

DISCUSSION

In this study on the extent of diagnostic delay of pulmonary embolism in primary care and its determinants, we observed that diagnostic delay was present in a substantial proportion of patients (26%). An important factor associated with diagnostic delay appeared to be the absence of the typical "text book" chest pain symptoms as presented during the first presentation at the general practitioner. Furthermore, in those with diagnostic delay, a respiratory tract infection was frequently reported, before the initial PE diagnosis was established.

This is one of the first studies on the magnitude of diagnostic delay of pulmonary embolism in a primary care setting. Strength of this study is the fact that we had access to the general practitioner's electronic patients records, including all consultations with the GP prior to the diagnosis, plus the correspondence between GPs and hospital specialists and all results from laboratory and imaging tests performed. This allowed us to sketch a complete and detailed picture of the diagnostic pathway starting from the first presentation of patients with signs and symptoms at their GP to the final diagnosis of PE.

However, for full appreciation of these results, some limitations need to be addressed. Foremost, we used a retrospective design to quantify diagnostic delay, which incurs several challenges.

First, we had to rely on correct ICPC-coding in all primary care practices. Only cases with the ICPC-code K93 were extracted for detailed assessment, leaving the chance of erroneously leaving out PE cases that were labelled with an incorrect ICPC-code. This could be the case if a patient is referred to secondary care with non-specific complaints like dyspnoea, consequently coded as such, without updating of the coding to PE afterwards. We however believe that this miscoding will be present only in a fraction of all PE cases, given that PE is an important diagnosis to be reported for further anticoagulant use and because of its prognostic implications. Another reason for incomplete selection of PE cases is the fact that patient records of those deceased were not available for all. This leaves the chance of missing PE events in patients that occurred in the years prior to their passing.

Second, data on determinants like oxygen saturation, heart rate and D-dimer levels were not reported in the patient records of many cases. For the current analyses, we assumed that the variable was not present if information on that item was not reported. However, it cannot be said for sure if these variables were not measured at all, or absent if not reported. Especially if PE is not suspected by the GP, it can be expected that not all PE risk factors and signs (e.g. recent traveling or respiratory rate) are explicitly asked. If so, this can lead to selective underreporting of specific determinants. In an attempt to gain insight into the possible selective reporting, we performed a sensitivity analysis in which we tested for the distribution of non-reported factors between the patients with and without delay. No substantial differences were observed, however (data not shown).

Third, we had to make interpretations on the relevance of certain complaints for the diagnosis PE, all with current knowledge that PE was indeed present. Blinding can only be achieved with extensive measures in a retrospective design, for example using patients with other final diagnoses as controls. In further research such blinding strategies should be considered.

Fourth, we used data from six different GP practices with distinct patient characteristics. Given the small number of cases, and the even smaller number of delayed cases, per practice, we decided not to assess practice effects on top of our first two models. Nevertheless, the extent of diagnostic delay seems to be rather homogenous (around 30%) across the practices under study and therefore we believe that our inferences are likely to be generalizable to at least primary care practices working in a similar healthcare setting like the UK, Ireland and Scandinavia.

Nevertheless, being aware of all these drawbacks of using a retrospective study design, we deemed this design to be the most suitable method to study delay in diagnosis. By definition, delay is only to be determined with hindsight and as a consequence, prospective evaluation of the diagnostic process will be difficult for a disease with a relatively low incidence in primary care.

We arbitrarily defined diagnostic delay as a time lag of >7 days between the first presentation at the GP and the final diagnosis. However, a lag period of >7 seven days can be deemed to be too large, especially considering the potential fatal outcome of not treating a PE event in time. (5) Therefore, we performed a sensitivity analysis in which we set the definition of diagnostic delay at 1 or more GP contact without adequate referral to secondary care for further diagnostics. Using this (more stringent) definition of diagnostic delay, the proportion of cases missed increased to over 40% (see Supplementary Material). Yet, the inferences on our reported determinants of delay remained rather constant, strengthening the validity of our findings.

Another complicating factor in the definition of delay in PE diagnosis concerns its physiological development and progression. In recent years, much has been written on the interplay of inflammation and an activated thrombogenic state. (15, 16) Thus, an infection could also be the precursor of, and provoking factor for, PE. An initial diagnosis of a respiratory tract infection that turns out to be a PE a few days later is not necessarily a delayed PE diagnosis. Instead, the PE can rather be the result of a cascade initiated by the infection. This distinction between a PE initiated by an infection, and a PE incorrectly diagnosed as an infection, cannot be made easily, leaving the chance of overestimation of the association between diagnostic delay and a respiratory tract infection. This possible interplay between infection and venous thrombosis was also observed the other way around in a recent case control study by Timp and colleagues including over 2500 VTE patients. (17) Patients receiving antibiotics (as a proxy for infectious disease) had an increased risk of both first and recurrent VTE (incidence rate ratio (IRR) 5.6 (95% CI 4.6-6.8); 127 VTE patients while on antibiotics). Analogue to our inferences, this point estimate may have been too high due to misclassification of PE symptoms as an infection, and thus inappropriate prescription of antibiotics. After exclusion of those patients in whom misclassification was very likely, the IRR remained 5.0 (95% CI 4.0-6.1). The latter in fact would be classified as delay in diagnosis in our study.

In seven PE cases without diagnostic delay, the diagnosis of PE was not considered initially by the GP. However, due to the suspicion of another serious condition (acute coronary event), urgent referral to the emergency department led to prompt diagnosis of PE anyhow. In the strict sense of the definition, the diagnosis PE is missed here since it was not the diagnosis deemed to be most likely by the GP. We treated these missed, but adequately referred, cases as "delay present" in a sensitivity analysis, not changing our inferences (data not shown).

Finally, we did not collect data on the clinical implications of diagnostic delay, like quality of life or long-term health effects. However, knowledge on the impact of delay on clinical outcomes is important to be able to value the relevance of delayed diagnoses: it can be hypothesized that long-term outcomes are worse for patients who have had a prolonged duration of complaints, caused by the lengthened exposure to vessel obstruction, and consequent vessel damage, pulmonary hypertension or lung infarction. Further prospective research however is needed to address this research question for the primary care domain.

Comparison with other studies

A few studies on delay in diagnosis of pulmonary embolism have been performed in secondary care, especially in emergency departments. For example, Torres-Macho et al. found that diagnostic delay was present in 146/ 436 (33.5%) PE cases at a Spanish emergency department. Patients were older (71.5 years (SD 15.2) vs 67.3 years (SD 13.7) (P= 0.04)) and had more frequently COPD (29.7% vs 7.25 (P=<0.001)) or asthma (11.7% vs 4.1% (P=0.01)) if PE was diagnosed during hospitalization after ED examination. Patients who were sent home with a wrong diagnosis, presented more often with a cough (25.9% vs. 13.4% (p= 0.01)) and fever (18.5% vs. 5.1% (p=0.002)). (8) In the study by Alonso- Martinez and colleagues, a delay in diagnosis longer than 6 days was present in 50% of cases (186/ 375 patients). The number of days of delay was higher amongst elderly (median days of delay 7 (IQR 13) if age ≥65 vs. 4 (IQR 5) if age <65 years (p=<0.01)), and in those with previous cardiac disease and without sudden onset of dyspnoea. (6) In our study, older age was associated with diagnostic delay too, just like the absence of typical PE complaints. However, female gender was not reported previously in relation with delay. Only one study mentioned female gender as a risk factor for

patient-delay rather than doctor-delay. (13) Given our small sample size and exploratory nature, these findings require further evaluation in future research. A recent retrospective study was conducted in a Dutch secondary care setting in which delay in primary care was estimated as well. Whereas 75% of patients were referred within one day, the remaining 25% had an average delay of 15.7 days. (14) One important determinant for early referral was the presence of chest pain. This is in line with our results, in which the absence of chest symptoms was associated with diagnostic delay.

Clinical implications

Given the substantial percentage of cases with delay in diagnosis of PE observed in this current study, we assume that most GPs come across a situation with diagnostic delay in PE regularly. Even if an alternative diagnosis is confirmed (e.g. infiltrate on chest radiography, or an initial improvement after the initiation of antibiotic treatment), PE can be present simultaneously, or develop along the course of the concurrent disease. Therefore, we argue that an initial diagnosis should be reconsidered frequently, especially if symptoms do not improve as much as can be expected, and in those with coexisting cardiopulmonary conditions.

Furthermore, we showed in this current study that the diagnosis of PE is more often delayed in case of non-typical presentation of complaints. Therefore, we suggest GPs to consider PE as a potential diagnosis even if symptoms are not overwhelmingly pointing into that direction. To prevent an overshoot of referrals to secondary care as a consequence of this low threshold of suspicion, a diagnostic prediction model might help GPs to further guide the decision whether or not to refer a patient. (18) Nevertheless, especially in elderly and those with concurrent respiratory tract infections, the false-positive rate of these prediction models

(specifically the D-dimer test) is considerable. (19, 20) As such, the optimal balance between raised awareness of PE and refraining from over-referral has yet to be found and further evaluation of diagnostic delay is needed.

CONCLUSION

Diagnostic delay of pulmonary embolism is common in primary care, especially if classical PE symptoms like chest complaints are absent. Awareness of the possibility of a PE being the underlying cause of a wide range of symptoms, might contribute to a reduction of the number of delayed PE diagnoses in primary care.

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Author's contribution

Conception and design of the work (JH, GJG, KM), data collection (JH, MK-vR, MM, GJG), data analysis and interpretation (JH, MK-vR, MM, GJG, KM), drafting the article (JH, MK-vR, MM, GJG), critical revision of the article (RS, RO, KM), final approval of the version to be published (JH, MK-vR, MM, RO, RS, KM, GJG)

Data sharing statement

The dataset and statistical codes are available from the authors upon request.

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Table 1- Characteristics of patients with and without GP visit before diagnosis PE

	No prior GP visit (n=49)	**Prior GP contact(s)** (n=128)	**p-value**
Age in years***, mean (± SD)	60 (17)	58 (16)	0.429
Male gender	27 (55)	60 (47)	0.327
Comorbidity			
COPD/ asthma	5 (10)	27 (21)	0.067*
Hypertension	11 (22)	37 (29)	0.387
Atrial fibrillation	1 (2)	4 (3)	1.000*
Congestive heart failure	0 (0)	6 (5)	0.189*
Ischemic heart disease	3 (6)	14 (11)	0.406*
Risk factors			
History of DVT	7 (14)	26 (20)	0.357
Recent surgery	8 (16)	8 (6)	0.045*
Recent immobilization	4 (8)	6 (5)	0.467*
Recent travelling	2 (4)	4 (3)	0.669*
Malignancy	9 (18)	10 (8)	0.042
Estrogen use, women	0/22 (0)	19/68 (28)	0.005*
Prior pulmonary infection	3 (6)	23 (18)	0.057*
History of smoking	6 (12)	33 (26)	0.052
Pregnancy	0/22 (0)	3/68 (4)	1.000
Days until diagnosis, median [IQR]	0 [0]	1 [8]	
total range	NA	0-126 days	
Delay > 7 days	NA	33 (26)	

Values are numbers (percentages) unless stated otherwise. *Fisher's exact test *** missing values (n=3)
PE= pulmonary embolism; GP= general practitioner; SD= standard deviation; COPD= chronic obstructive pulmonary disease; DVT= deep venous thrombosis; IQR= interquartile range; NA= not applicable.

Table 2- Baseline characteristics *(diagnostic delay >7 days)*

	No diagnostic delay (n=95)	**Diagnostic delay > 7 days** (n=33)	**p-value**
Age in years***, mean (± SD)	56 (15)	62 (18)	0.068
Age >75 years	12 (13)	15 (46)	<0.001
Male gender	47 (49)	13 (39)	0.317
Symptoms			
Dyspnea	62 (65)	22 (67)	0.884
Chest complaints	59 (62)	9 (27)	0.001
Chest pain	51 (54)	8 (24)	0.003
Painful respiration	31 (33)	3 (9)	0.011*
Cough	17 (18)	12 (36)	0.029
Hemoptysis	3 (3)	1 (3)	1.000*
Signs of DVT	18 (19)	1 (3)	0.025*
Fever (>38°C)	5 (5)	2 (6)	1.000*
Collapse	4 (4)	0 (0)	0.572*
Heart rate, mean (± SD)	96 (19)	95 (26)	0.916
O_2 saturation, median [IQR]	96 [5]	94 [9]	0.124
Comorbidities			
COPD and/or asthma	14 (15)	13 (39)	0.004
Hypertension	25 (26)	12 (36)	0.273
Atrial fibrillation	2 (2)	2 (6)	0.273*
Congestive heart failure	3 (3)	3 (9)	0.177*
Ischemic heart disease	10 (11)	4 (12)	0.755*
Risk factors			
History of DVT	18 (19)	8 (24)	0.515
Recent surgery	7 (7)	1 (3)	0.679*
Recent immobilization	6 (6)	0 (0)	0.338*
Recent travelling	4 (4)	0 (0)	0.572*
Malignancy	7 (7)	3 (9)	0.717*
Estrogen use, women	15/48 (31)	4/20 (20)	0.393*
Prior pulmonary infection	12 (13)	11 (33)	0.008
History of smoking	26 (27)	7 (21)	0.486
Pregnancy	3/48 (6)	0/20 (0)	0.550

Values are numbers (percentages) unless stated otherwise. *Fisher's exact test *** missing values (n=3)
PE= pulmonary embolism; SD= standard deviation; DVT= deep venous thrombosis; IQR= interquartile range; COPD= chronic obstructive pulmonary disease; NA= not applicable.

Table 3a- Multivariable logistic regression model for the association between signs and symptoms with a diagnostic delay > 7 days

MODEL 1	OR (95%CI)	p-value
Female gender	2.5 (0.9 - 6.6)	0.071
Age >75	5.1 (1.8 - 14.1)	0.002
No chest complaints	5.4 (1.9 - 15.2)	0.002
No dyspnea	2.3 (0.8 - 6.5)	0.118

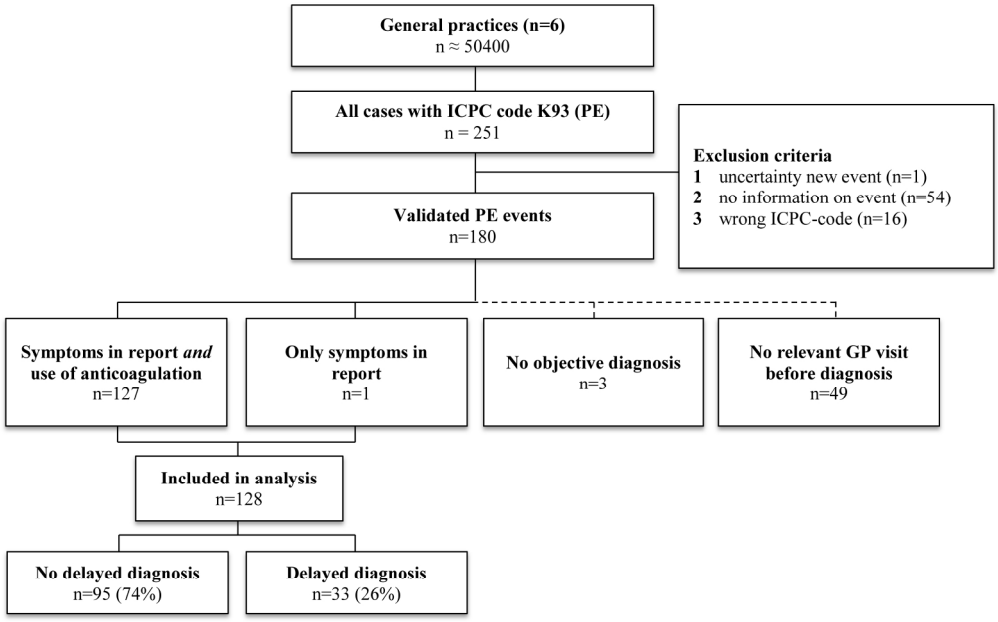
OR= odds ratio; 95%CI= 95% confidence interval.

Table 3b- Multivariable logistic regression model for the association between signs, symptoms and comorbidity with a diagnostic delay >7 days

MODEL 2	OR (95%CI)	p-value
Female gender	3.1 (1.1 - 8.8)	0.036
Age >75	4.3 (1.5 - 12.3)	0.007
No chest complaints	5.4 (1.8 - 16.1)	0.003
No dyspnea	3.1 (1.0 - 9.4)	0.047
Prior respiratory tract infection	3.3 (1.1 - 10.0)	0.031
COPD/asthma	3.3 (0.9 - 7.5)	0.085

OR= odds ratio; 95%CI= 95% confidence interval.

Figure 1- Flow chart of the selection of pulmonary embolism cases in primary care



PE= pulmonary embolism; ICPC= international classification of primary care; GP= general practitioner

191x145mm (300 x 300 DPI)

Supplementary Material

Table 1- Baseline characteristics *(diagnostic delay >1 relevant GP contact)*

	No diagnostic delay (n=71) **(55.5%)**	**Diagnostic delay > 1 GP contact** (n=57) **(44.5%)**	**p-value**
Age in years***, mean (± SD)	57 (15)	58 (17)	0.068
Age >75 years	11 (15)	16 (28)	0.083
Male gender	31 (44)	29 (51)	0.416
Symptoms			
Dyspnea	50 (70)	34 (60)	0.202
Chest complaints	49 (69)	19 (33)	<0.001
Chest pain	43 (61)	16 (28)	<0.001
Painful respiration	27 (28)	7 (12)	0.001*
Cough	11 (16)	18 (32)	0.031
Hemoptysis	2 (3)	2 (4)	1.000*
Signs of DVT	12 (17)	7 (12)	0.465
Fever (>38°C)	3 (4)	4 (7)	0.699*
Collapse	4 (6)	0 (0)	0.128*
Heart rate, mean (± SD)	96 (20)	92 (22)	0.916
O_2 saturation, median [IQR]	96 [5]	94 [6]	0.124
Comorbidities			
COPD and/or asthma	9 (13)	18 (32)	0.009
COPD	8 (11)	8 (14)	0.638
asthma	1 (1)	11 (19)	0.001
Hypertension	24 (34)	13 (23)	0.173
Atrial fibrillation	2 (3)	2 (4)	1.000*
Congestive heart failure	3 (4)	3 (5)	1.000*
Ischemic heart disease	8 (11)	6 (11)	0.894
Risk factors			
History of DVT	16 (23)	10 (18)	0.485
Recent surgery	5 (7)	3 (5)	0.732*
Recent immobilization	5 (7)	1 (2)	0.225*
Recent travelling	2 (3)	2 (4)	1.000*
Malignancy	6 (9)	4 (7)	1.000*
Estrogen use, women	13/40 (33)	6/28 (21)	0.317*
Prior pulmonary infection	7 (10)	16 (28)	0.008
History of smoking	18 (25)	15 (26)	0.901
Pregnancy	3/40 (8)	0/28 (0)	0.263*

Values are numbers (percentages) unless stated otherwise. *Fisher's exact test *** missing values (n=3) PE= pulmonary embolism; SD= standard deviation; DVT= deep venous thrombosis; IQR= interquartile range; COPD= chronic obstructive pulmonary disease; NA= not applicable.

Supplementary Material

Table 2a- Multivariable logistic regression model for the association between signs and symptoms with a diagnostic delay **> 1 GP contact**

MODEL 1	**OR (95%CI)**	**p-value**
Female gender	1.1 (0.5 - 2.5)	0.788
Age >75	1.9 (0.7 - 5.0)	0.215
No chest complaints	5.7 (2.4 - 13.7)	<0.001
No dyspnea	3.2 (1.3 - 7.8	0.012

OR= odds ratio; 95%CI= 95% confidence interval.

Table 2b- Multivariable logistic regression model for the association between signs, symptoms and comorbidity with a diagnostic delay **> 1 GP contact**

MODEL 2	**OR (95%CI)**	**p-value**
Female gender	1.3 (0.5 - 2.9)	0.589
Age >75	1.4 (0.5 - 3.9)	0.515
No chest complaints	5.4 (2.1 - 13.5)	<0.001
No dyspnea	3.7 (1.5 - 9.4)	0.006
Prior respiratory tract infection	3.4 (1.1 - 9.9)	0.028
COPD/asthma	2.4 (0.8 - 6.7)	0.100

OR= odds ratio; 95%CI= 95% confidence interval.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item	Recommendation		Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	✓	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	✓	3
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	✓	7-8
Objectives	3	State specific objectives, including any prespecified hypotheses	✓	8
Methods				
Study design	4	Present key elements of study design early in the paper	✓	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	✓	8-10
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	✓	8-10
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n.a.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	✓	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	✓	9-10
Bias	9	Describe any efforts to address potential sources of bias	✓	9-11
Study size	10	Explain how the study size was arrived at	✓	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	✓	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	n.a.	
		(*c*) Explain how missing data were addressed	✓	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	✓	9
		(*e*) Describe any sensitivity analyses	✓	11

Continued on next page

Results				**Page**
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	✓	12-13
		(b) Give reasons for non-participation at each stage	✓	12-13
		(c) Consider use of a flow diagram	✓	27
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	✓	12-13
		(b) Indicate number of participants with missing data for each variable of interest	✓	27
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n.a.	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	✓	12-13
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	✓	13
		(*b*) Report category boundaries when continuous variables were categorized	n.a.	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	✓	28-29
Discussion				
Key results	18	Summarise key results with reference to study objectives	✓	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	✓	13-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	✓	15-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	✓	15
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	✓	5-6

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.