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Syncope, the "Forgotten-Sign" of a Life-Threatening Pulmonary Embolism

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ABSTRACT
Pulmonary embolism (PE) is one of the most common forms of venous thromboembolism (VTE), with a relatively high annual incidence of approximately 39–115 per 100,000 population. Given its widely variable clinical presentations, PE can be life-threatening if not recognized and treated early. Syncope is a relatively common and clinically important presentation of PE; however, in daily practice, it is often not immediately considered in the differential diagnosis. We reported a case of a 37-year-old male who complained of sudden blackout and a sensation of near-fainting, with a history of shortness of breath following mild daily activities, which was later diagnosed as PE with a D-dimer level of >10 µg/mL. The addition of fondaparinux to his treatment regimen significantly improved his condition. The prognosis of patients depends on the underlying pathology, patient risk factors, duration from symptom onset to hospital admission, and the use of thrombolytic agents. This case report was prepared to increase clinicians' awareness of PE as a potential cause of syncope, in order to prevent life-threatening complications.

INTRODUCTION

Pulmonary embolism (PE) is a condition characterized by a sudden blockage in the pulmonary blood vessels. PE is one of the most common forms of venous thromboembolism (VTE). When a thrombus, such as one originating in the deep veins of the leg or pelvis, dislodges, it becomes an embolus and can travel to the lungs through the bloodstream (National Institute for Health and Care Excellence [NICE], n.d.). There are more than 250,000 hospitalizations in the United States due to VTE each year (Demircan et al., 2009), with a mortality rate exceeding 15% within the first three months after diagnosis (Piazza & Goldhaber, 2006). A 2004 study across six European countries reporting VTE-related deaths found that 34% of patients died before therapy could be initiated; 59% of deaths were due to PE diagnosed post-mortem, and only 7% were correctly diagnosed prior to death (Konstantinides et al., 2020). According to previous reports, patients diagnosed with PE within 48 hours of emergency department (ED) arrival had improved outcomes, and those who received anticoagulant therapy within 24 hours of ED arrival had reduced mortality rates (Smith et al., 2012). Patients with PE may present with a wide range of clinical manifestations and can develop life-threatening conditions (NICE, n.d.).

The clinical presentation of PE varies widely (Kranidis et al., 2006), with dyspnea being the most frequent symptom and tachypnea the most common sign. Patients without underlying cardiopulmonary disease may appear anxious, while those with massive PE may present with

hypotension, cardiogenic shock, or cardiac arrest (Piazza & Goldhaber, 2006; Prandoni et al., 2016). Small distal emboli may cause areas of alveolar hemorrhage, which can present as hemoptysis (Konstantinides et al., 2020).

The principal challenge in managing PE lies in its early diagnosis. Clinical manifestations are highly variable and often nonspecific, ranging from dyspnea, chest pain, and hemoptysis to severe presentations such as cardiogenic shock and cardiac arrest. This broad spectrum frequently leads to delayed recognition and underdiagnosis (Gellert et al., 2025; Slade et al., 2018). Several European studies have reported that more than half of PE-related deaths were identified only through post-mortem examinations, while only a small proportion of cases were correctly diagnosed prior to death. These findings highlight persistent challenges in clinical awareness and timely diagnosis of PE (Kwok et al., 2022; van Maanen et al., 2022; Zuin et al., 2024).

One of the most overlooked clinical manifestations of PE is syncope or presyncope. Pathophysiologically, syncope in PE may occur through several mechanisms. First, extensive pulmonary vascular obstruction increases right ventricular pressure, reduces left ventricular filling, and subsequently decreases cardiac output, leading to sudden cerebral hypoperfusion (Giannakoulas et al., 2025; Rosenkranz et al., 2020). Second, PE may precipitate cardiac arrhythmias that cause hemodynamic instability and impaired cerebral perfusion. Third, the embolic event itself may trigger a vasovagal reflex, resulting in hypotension and transient loss of consciousness. Despite these well-established mechanisms, syncope is rarely considered an initial manifestation of PE in routine clinical practice (Hogan et al., 2016; Ilyas et al., 2026; Middleton et al., 2015).

Conceptually, the diagnosis of PE is based on clinical probability assessment, which integrates risk factors, clinical findings, laboratory results, and imaging studies. Clinical tools such as the Modified Wells Criteria and the Simplified Pulmonary Embolism Severity Index (sPESI) are used to estimate the probability and severity of PE. D-dimer testing has high sensitivity and serves as an effective initial screening tool, whereas computed tomography pulmonary angiography (CTPA) remains the gold standard imaging modality for confirming the diagnosis. Furthermore, early recognition and prompt initiation of anticoagulant therapy in patients with intermediate-to-high probability of PE can significantly reduce mortality and prevent life-threatening complications.

Despite established diagnostic and therapeutic guidelines, a considerable gap remains between recommendations and clinical practice, particularly in cases of PE presenting with syncope. Previous studies have mainly focused on syncope from neurological or cardiogenic perspectives, while reports describing syncope as an initial manifestation of PE remain limited. Moreover, studies integrating patient risk factors, pathophysiological mechanisms, diagnostic processes, and therapeutic responses in PE patients presenting with syncope are still scarce, especially in the Indonesian healthcare setting.

The novelty of this study lies in its comprehensive analysis of syncope as a “forgotten sign” of life-threatening pulmonary embolism. This study not only describes an atypical clinical presentation of PE but also evaluates the relationship between patient risk factors, the sequential use of diagnostic modalities, and the effectiveness of early anticoagulant therapy in improving clinical outcomes. Consequently, this study provides a new perspective on the

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importance of considering PE in the differential diagnosis of patients presenting with syncope or presyncope.

Therefore, this study aims to analyze syncope as an overlooked clinical manifestation of pulmonary embolism, identify factors underlying its occurrence, and evaluate the importance of early recognition and prompt management in preventing complications and mortality associated with pulmonary embolism.

METHOD

This study employed a qualitative intrinsic case study design to obtain an in-depth understanding of syncope as an atypical clinical manifestation of life-threatening pulmonary embolism (PE). The case study design was used because it enabled a comprehensive exploration of this complex clinical phenomenon within its real-life clinical context, particularly when the boundaries between the phenomenon and its context were not clearly defined.

RESULT AND DISCUSSION

A-37-year-old male, seek consultation with our neurologist due to a sudden blackout and feeling about to pass-out, after he went to the toilet. In the past three days prior to his visit, he experienced shortness of breath after mild-daily activities, with no chest pain. He then got admitted on 29th of May for further work-up for neurogenic/cardiogenic-induced presyncope and treatment. He had a past medical history of a low-grade astrocytoma and was advised for radiotherapy, but he had not. His profile was obese, with 1.7m in height and weight for 112kg, with initially normal blood pressure, tachycardic 122 beats per minute, respiratory rate of 23 times per minute, and pulse oxygen saturation was 94% with 2L of oxygen. His initial blood test showed slightly elevated leukocyte 11.5, and CRP level 49.6 mg/dL (normal <5).

The night of his admission, his shortness of breath worsens and his oxygen saturation dropped. Then he was consulted to our cardiologist, and was suspected for pulmonary embolism. Echocardiography showed RV dilatation with hyperdynamic base, ejection fraction of 55%, LV diastolic can't be measured due to tachycardia, and also moderate tricuspid regurgitation. He was given Furosemide extra of 20mg intravenously, and while waiting for other blood test and computer tomography pulmonary angiography (CTPA), he was moved to High Care Unit for close observation. His prothrombin time (PT) and activated prothrombin time (APTT) result came out and were slightly prolonged, 10.9 (10.6) s and 28.0 (27.3) s respectively, with international normalized ratio (INR) of 1.05, normal Troponin T level, and a high D-Dimer result of >10ug/mL (normal <0.05 ug/mL), so we added Fondaparinux 1x7.5mg subcutaneously to his medication regiment. Later on, his CTPA imaging showed thrombus at the distal of both of the main pulmonary, branch A, and both of the basal trunks *(Figure 1).* After just one day of Fondaparinux addition to his regiment, even though he'd still catch his breath while talking, but overall his shortness of breath improved, and no longer experience lightheadedness. On the next day, June 1st, our cardiologist also performed ultrasonography on his lower extremities and found thrombus on his left femoral, and severe insufficiency in the superficial vein of right leg, so the patient was asked to wear compression stocking every morning-evening. Based on observation in the high care unit for around 3 days, his symptoms improved significantly and was moved back to the ward.

His coagulation profile was evaluated on June 6th and showed improvement. His previously prolonged PT, was down to 10.5 (10.4), APTT 21.8 (24.1), with D-dimer dropped to 6.06. We also evaluated thee ultrasound of his lower leg which thrombus has reduced. He was treated in the ward until he's okay and stable enough with no oxygen support, and after went through a 6-minutes walk test. Then he was discharged from the hospital with take-home oral anticoagulant, and other symptomatic medication.

We followed-up the patient when he visited our cardiologist and neurologist in the clinic, around 1 week after being discharged. He no longer experienced shortness of breath nor lightheadedness/blackout feeling, and his D-dimer level was down to 2.21, and 1.6 respectively on the following two-weeks.

It's believed that diagnosing a PE is more challenging than treating one (Kranidis et al., 2006). His complain of sudden blackout and feeling about to pass-out was defined as presyncope (near-syncope) (Whitledge et al., 2024), with the previous history of shortness of breath that worsen on the night of his hospital admission, led us to the suspicion of PE. A lot of conditions were collected and listed as the predisposing environmental and genetic factors for VTE (Konstantinides et al., 2020). In our case, the patient was known to have a low-grade astrocytoma, a smoker, and was obese. Using the Modified Wells Criteria (Boka et al., 2020), with heart rate >100 during initial assessment (1.5 point) and history of malignancy (1 point), his probability of PE was unlikely. According to the guideline (Konstantinides et al., 2020), he had two moderate risk factors (cancer and pneumonia) and obesity as his weak risk factor, and his simplified Pulmonary Embolism Severity Index (sPESI) (Konstantinides et al., 2020) score was 2.

Syncope, as one of the most common differential diagnosis of PE, in daily practices, is rarely considered as one(Prandoni et al., 2016; Suwanwongse & Shabarek, 2020). If syncope is associated with total occlusion of the pulmonary vessel, it progresses to cardiac arrest and death, but in other cases, syncope can be brief with a transient hypotension, because the occlusion is partial(Altınsoy et al., 2016). There are at least three possible mechanism of PE-induced syncope, the first one is when the occlusion of pulmonary vessel (>50%) leads to RV and LV impairment and causing sudden drop of cardiac output and cerebral blood flow (Altınsoy et al., 2016; Prandoni et al., 2016; Suwanwongse & Shabarek, 2020). Second, PE may be induced by arrhythmias (cardiogenic syncope), and third, the embolus itself may provoke vasovagal reflex and neurogenic syncope(Suwanwongse & Shabarek, 2020). As for cardiogenic syncope, the main cause is due to rhythm disturbance, that can cause hemodynamic instability that leads to decreased cardiac output thus disturbs the cerebral blood flow(Читателям et al., n.d.). Most patients suffering from acute PE, present with one of the three different clinical syndromes, which are pulmonary infarction, acute unexplained dyspnea, and acute cor-pulmonale(Demircan et al., 2009; Prandoni et al., 2016). Pulmonary infarction syndrome happens with a submassive embolism that totally blocks the distal branch, and resulting with pleuritic chest pain, hemoptysis, rales, and abnormal chest x-ray. In acute, unexplained dyspnea pattern, also happens due to the same reason, but mostly have normal chest x-ray and ECG, but with low pulse oxygen saturation. In the third pattern, acute cor-pulmonale, there's a 60-75% obstruction of pulmonary circulation, thus the patient experience shock, syncope, or sudden death(Demircan et al., 2009; Prandoni et al., 2016). Our patient

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haemodynamic status was relatively stable, so we assessed further of his risk stratification according to the guideline.

Laboratory test of D-dimer and fibrinolysis should be evaluated as they offer a high sensitivity and high negative predictive value for patients suspected of PE, especially in ED setting. Electrocardiography (ECG) may show RV strain, S1Q3T3, but can also be normal, especially in younger patients(Piazza & Goldhaber, 2006b; Prandoni et al., 2016), or in 40% cases showed sinus tachycardia in milder cases(Konstantinides et al., 2020) like in our patient that showed tachycardia. We found RV dilatation with hyperdynamic base from his echocardiography. Imaging study is needed, especially for inpatients who might have comorbid conditions. Pulmonary angiography was the gold standard for the diagnosis, but it's an invasive procedure and not readily available in all centers. Computed tomographic pulmonary angiography (CTPA), which available in most centers, is a more reasonable method of choice to visualize the pulmonary vasculature(Konstantinides et al., 2020; Kranidis et al., 2006).

Right after his elevated D-dimer and normal cardiac enzyme result came out, he was classified as intermediate-low risk of PE(Konstantinides et al., 2020), he then received fondaparinux, an anticoagulant medication, injected subcutaneously, without waiting for the imaging result. The administration of anticoagulant in patients with high or intermediate probability of PE should be initiated right away, with either weight-adjusted low-molecular weight heparin (LMWH) or fondaparinux, or intravenously with unfractionated heparin (UFH)(Konstantinides et al., 2020). Due to lower risk of inducing major bleeding and heparin-induced thrombocytopenia, LMWH and fondaparinux are preferred over UFH(Konstantinides et al., 2020; Whitledge et al., 2024). According to the guideline, UFH nowadays largely restricted to patients with obvious hemodynamic instability, and whom will need primary reperfusion treatment , and also those with severe renal impairment (of creatinine clearance <= 30ml/minute)(Konstantinides et al., 2020).

Supporting his CTPA result from his leg ultrasonography, our cardiologist found thrombus on the left femoral, with severe insufficiency in the superficial vein of right leg. In the majority of PE cases, up to 70% of it, originates from a DVT in a lower limb. Ultrasound of the leg supports the diagnosis of PE(Piazza & Goldhaber, 2006a; Prandoni et al., 2016). Finding a proximal DVT in patients suspected with PE, considered enough to warrant anticoagulant treatment, without further testing, but still requires risk assessment for PE severity and risk of early death(Konstantinides et al., 2020). Parallel with UFH, LMWH or fondaparinux, a Vitamin K antagonist (VKAs), which have been the gold standard, should be used for at least 5 days, and until the INT normalized.
For high-risk PE patient, they may benefit more and improve faster with reperfusion treatment, which can be a systemic thrombolysis, a percutaneous catheter-directed treatment, or a surgical embolectomy(Konstantinides et al., 2020).

CONCLUSION

Pulmonary embolism is a potentially fatal condition that presents with a wide range of signs and symptoms (Castelli et al., 2003). Although PE is a differential diagnosis in patients presenting with syncope, current evidence indicates that it is not always considered in clinical practice. PE presenting with syncope is particularly challenging to diagnose, as this symptom may represent a "forgotten sign" of life-threatening PE (Altınsoy et al., 2016; Badertscher et

al., 2019). Further laboratory tests and imaging studies are essential to support the diagnosis and to minimize the risk of both under-treatment and over-treatment. The prognosis of patients depends on the underlying pathology, patient risk factors, duration from symptom onset to hospital admission, and the use of thrombolytic agents (Altınsoy et al., 2016; Badertscher et al., 2019).

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