# Life expectancy in cancer patients with pulmonary thromboembolism: From clinical prognostic biomarkers and paraclinical investigations to therapeutic approaches (Review)

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**Abstract.** Pulmonary embolisms (PEs) are obstructions of the pulmonary arteries by thrombi, which are emboli and they most frequently originate from the deep venous system of the inferior limbs. Emboli can also come from the inferior vena cava, abdominal and pelvic veins, or the upper body venous system from the right atrium or ventricle of the heart. Thrombi can form *in situ* inside pulmonary arteries as well. A cancer patient is at a higher risk for thromboembolic phenomena given both the oncological pathological context and also due to the associated medical or surgical treatment they receive. PE is a high-risk medical emergency that is associated with an increased risk of early mortality, with sudden death occurring in 25% of patients. The long-term presence of this condition can result in thromboembolic pulmonary hypertension. The risk of mortality, both in the acute and long-term, is dependent on the severity of the acute form, the recurrence of the embolism and the associated conditions. The majority of deaths associated with PE can be prevented by early diagnosis. The aim of the present review was to describe the various biological and cellular parameters, together with known paraclinical investigations, to assist in the rapid diagnosis of PE. Mortality in patients with PE and neoplastic conditions may be reduced by initiating anticoagulant treatment as soon as possible. PE may be the first manifestation of an underlying silent malignancy or may represent a complication of an already diagnosed malignancy. Exclusion or confirmation of the diagnosis is of utmost importance to avoid unnecessary anticoagulant treatment associated with a high risk of bleeding or to start immediate anticoagulant treatment if required.

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**Contents**



## 1. Introduction

Pulmonary thromboembolism (PE) represents a serious condition and is a significant cause of mortality worldwide. This has led to an increase in research studying predictive prognostic factors to improve mortality rates. Several factors have been identified including major trauma and surgery, hip or knee prosthesis, fractures, prolonged immobilization, malignancy, the use of oral contraceptives or hormonal substitution therapy and pregnancy, all of which can lead to a worse prognosis (1,2).

Patients with cancer have an eight-fold increased risk of PE compared with healthy individuals (3,4). The incidence of embolic events differs according to age, location of the malignancy, staging and histopathological features, as well as various hospital-related factors such as length of hospitalization, central venous catheters and administration of chemotherapy (3,5-7). For example, patients with pancreatic, lung, colorectal, prostate, breast, brain and hematological cancers exhibit a higher risk of PE. Similarly, patients with metastatic stomach, liver and lung neoplasia are more likely to develop a PE (3,5-7).

The evolution of these thromboembolic events differs by patient, therefore identifying prognostic parameters followed

by optimized treatment criteria can reduce morbidity and mortality. Biomarkers such as natriuretic peptides (NTproBNP and BNP), troponins (cTnT) and D-dimers have allowed for the stratification of PE into various subtypes, which can aid in the development of diagnostic and therapeutic regimens.

According to a study on a group of 100 patients with PE that assessed mortality, measurement of NTproBNP and troponin T biomarkers at the time of patient admission assisted with risk stratification. In patients with cancer with troponin T serum values >0.07 $\mu$g/l, the total mortality rate was 15% and the mortality rate by acute PE was 8%. Similarly, NTproBNP serum values >7,600 ng/l were predictive of mortality by any disease including acute PE (8). Mortality rates in patients with acute PE who had serum levels of NTproBNP ≥600 ng/l and T troponin serum values ≥0.07 $\mu$g/l were 33%. The mortality rate of patients with an NTproBNP serum level <600 ng/l and cTnT serum level <0.07 $\mu$g/l was found to be only 3.7% (8).

The aim of the present review was to provide a reference article for clinicians by summarizing the findings of data from multiple studies, including observational studies that evaluated the accuracy of diagnosing PE in patients with cancer and also to compare the effectiveness of different anticoagulant therapeutic regimens in a category of patients with a complex pathology, which often poses a significant challenge.

## 2. Clinical prognostic biomarkers and paraclinical investigations

Typically, the primary cause of PE is deep venous thrombosis (DVT), which is present in ~70% of patients diagnosed with PE (9,10). The incidence of DVT may vary according to the age and sex of patients, with it being more prevalent in men and the elderly (11). Emboli originating from the lower limb deep venous system are ten times more likely to migrate compared with emboli in the upper body.

A significant number of conditions present Virchow's triad (venous stasis, hypercoagulability state and injury of the vessel wall) (12), which may predispose an individual to PE and a patient with cancer typically presents with the following features: They are bedridden, often dehydrated, exhibit increased secretion of parathyroid hormone with a procoagulant effect and venous access is required for curative or palliative treatment (1,13). Predisposing factors to venous thromboembolism and PE are classified according to the associated risk level (1,2); high-risk predisposing factors include orthopedic surgery, hospitalization for heart failure or rhythm disturbances in the past 3 months, major trauma, recent myocardial infarction, or a history of venous thromboembolism. Moderate risk predisposing factors include minimally invasive orthopedic surgery, blood transfusions, central venous catheters, pacemakers, chemotherapy, congestive heart failure, respiratory failure, neoplasia, oral contraceptive medication, stroke, post-partum period, superficial venous thrombosis and thrombophilia. Low-risk predisposing factors include being bedridden for >3 days, diabetes mellitus, hypertension, prolonged trips by plane or vehicles, being elderly, minimally invasive surgery, obesity, pregnancy and chronic venous insufficiency.

An increasing number of cancer patients are exhibiting moderate risk factors and this is exacerbated by the cumulative effect of additional factors including dehydration, paraneoplastic syndromes, major resection surgery, multiple venous access points (port-a-cath and venous catheters) and chemotherapy. The type of malignancy markedly influences the risk for DVT and according to this, Khorana *et al* (14) developed a predictive model for DVT risk based on five factors (Table I): Site of cancer (2 points for very high-risk site, 1 point for high-risk site), platelet count of $350x10^9$/l or more, hemoglobin levels <100 g/l (10 g/dl) and/or use of erythropoiesis-stimulating agents, leukocyte count >$11x10^9$/l and a body mass index of ≥35 kg/m$^2$ (1 point each) (14).

These parameters were combined into a simple risk assessment model that allows providers to classify patients into three discrete categories corresponding to the risk of chemotherapy-associated venous thromboembolism (VTE; low-risk, 0; intermediate-risk, 1-2; and high-risk, >3 of VTE-0.3, 2 and 6.7%) and this classification could be used to assist in deciding the appropriate therapeutic regimen for thromboprophylaxis.

A literature review of articles published on Web of Science over the past 6 years (between January 2018 and January 2024) revealed articles indicating various cellular mechanisms of venous thrombotic events leading to PE. Chemotherapy was associated with bone marrow suppression and consequently thrombocytopenia. In cancers that pose an increased risk of DVT and consequently, therapeutic and preventative challenges, thrombocytopenia was associated with both the risk of thromboembolism and bleeding during anticoagulant treatment (15).

There is a paradox; 20-25% of patients with solid tumors of the pancreas (16), stomach, genitourinary tract, or brain (glioblastoma) (17) have thrombocytopenia, induced by platin-based chemotherapy (such as gemcitabine or temozolomide) which implicitly leads to an increased risk of bleeding (proportional to the severity of thrombocytopenia). Additionally, these same tumors are associated with a high incidence of developing PE. Thus, this category of patients requires safe and personalized therapeutic strategies. The selection of an appropriate type of anticoagulant treatment and the dose of this medication must be balanced with the risk of recurrence of PE and the risk of bleeding associated with thrombocytopenia due to chemotherapeutic treatment (15).

Another mechanism implicated in chemotherapy-induced thromboembolisms is the induction of arrhythmias, with an elongation of the QTc interval, necessitating the need for anticoagulant measures in these patients. Additionally, the use of central venous catheters on the same arm as lymphadenectomy is associated with an increased risk of thrombosis and it is recommended that a peripheral venous system is used in such cases (18). The facilitation of the release of specific tumor markers can increase the risk of DVT, as observed by Naito *et al* (19) in a study on colon cancer treated with polaprezinc, leading to an increase in CA19.9 levels.

The cellular mechanism of thrombosis induction involves the cytotoxic effect of chemotherapy through the release of lipoproteins, intracellular or cell membrane-related elements, which later serve as precipitating factors for subsequent thrombotic phases (20). Another implicated mechanism involves the activation of endothelial cells through elevated levels of von Willebrand factor and soluble P-selectin, secondary to the cytotoxic effect with the release of thrombospondin type 13.

Table I. Predictive model for chemotherapy associated venous thromboembolism (14).

| Item | | Risk score |
|---|---|---|
| Site of cancer: | Very high risk:<br>• Stomach<br>• Pancreas | 2 |
| | High risk:<br>• Lung<br>• Lymphoma<br>• Gynecologic<br>• Bladder,<br>• Testicular | 1 |
| Prechemotherapy platelet count ≥350x$10^9$/l or more | | 1 |
| Hemoglobin level <10 g/dl or use of red cell growth factors | | 1 |
| Prechemotherapy leukocyte count >11x$10^9$/l | | 1 |
| Body mass index ≥35 kg/$m^2$ | | 1 |

This endothelial cell activation triggers the cascade of intravascular thrombosis (21).

Chemotherapy can induce the establishment of inflammatory conditions triggering the NF-κB signaling pathway, leading to the production of proinflammatory cytokines. IL-6 enhances the procoagulant status by inducing tissue factor (TF) expression. TF expression initiates the coagulation system, characterized by increased D-dimer levels. A previous study evaluated the changes in plasma IL-6 and D-dimer levels in patients with cancer at a high risk of thrombosis undergoing chemotherapy (22). In serous ovarian cancers, Ward *et al* (23) identified a pronounced procoagulant effect of cisplatin and paclitaxel via the activation of the protein C pathway of coagulation.

Patients with cancer should be made familiar with the risk of such complications to raise awareness of the need for preventative medications and lifestyle adaptations, including adequate hydration and adopting an active lifestyle. Programs addressing this risk among patients exist (24).

Although DVT is responsible for ~75% of PE cases, there are other rare causes such as intracardiac thrombosis caused by arrhythmias, embolism with tumor fragments, septic embolism and iatrogenic causes (such as inferior vena cava filters or broken fragments of guiding devices) (1).

The highest risk of PE occurrence is within the first 12 months of neoplasia diagnosis, subsequently decreasing progressively after this period, approaching that of the general population after ~10 years. The increased risk in the first 12 months is associated with treatments such as chemotherapy and major surgical interventions (3,5,25). The annual incidence of VTE in patients receiving chemotherapy is estimated to be 11%, which can rise to 20% or higher depending on the drug(s) administered. In addition to chemotherapy, several other anti-neoplastic and supportive therapies are also associated with an increased risk of VTE development (17,26,27). Not every surgical treatment is associated with a high risk of PE. Surgical interventions involving prolonged bed rest and extensive resections associated with peripheral venous or pulmonary arterial vascular sutures are recommended against. An observational study by Sweetland *et al* (28), demonstrated that the risk of thromboembolism in patients undergoing orthopedic procedures (hip and knee replacement) is higher in the first 6 weeks postoperatively, surpassing that of cancer surgery. This study also suggests that the long-term risk of PE in patients with cancer may be up to eight times higher than other surgical treatments (28). Common symptoms and signs encountered in these patients include dyspnea, syncope, chest pain and hemoptysis (1). Massive PE, acute *cor pulmonale* (right ventricular dysfunction, acute heart failure, low cardiac output syndrome, hypoxemia) occurs due to increased pressure in the pulmonary artery above the mean pressure value (>40 mmHg), leading to the rapid development of pulmonary hypertension (1,13,29). Patients with sub-massive PE are hemodynamically stable and symptoms develop gradually. Pulmonary infarction occurs due to the obstruction of a peripheral pulmonary segmentary or sub-segmentary arterial branch (13).

Physical examination may reveal signs suggestive of the diagnosis: Distended jugular veins, hypotension, cardiogenic shock, tachycardia, paradoxical pulse, right ventricular gallop, tricuspid regurgitation systolic murmur, pleural friction rub and intensified vesicular sound, among others (1). Due to the nonspecific symptoms and physical examination, the European Society of Cardiology recommends the use of prediction scores (Wells and Geneva) for diagnosis, based on predisposing factors for DVT and PE (1). The issue of gastrointestinal cancers associated with cancer-related thrombosis, where anticoagulant administration is imperative has been addressed in a previous study where the role of low molecular weight heparin (LMWH) over oral anticoagulants was advocated for to avoid uncontrollable bleeding in the digestive system (30).

Once a PE has been established, paraclinical evaluation of the patient is performed in the same manner as in patients with cancer. Thus, laboratory analyses highlighting specific biomarkers of myocardial injury (NT-proBNP or troponins) can be altered due to right ventricular dysfunction resulting from sudden increases in pulmonary artery pressure (1). The levels of all biomarkers (NT-proBNP, D-dimer, myoglobin and troponins) are associated with right ventricular dysfunction (31,32). Elevated levels of NT-proBNP and troponins may be found in acute PE and are associated with the risk of PE-associated mortality (33-36). Normal NT-proBNP levels are predictive of a good prognosis (37-40). Increased troponin and myoglobin levels signify myocardial involvement, but there is no clear evidence that they are more significant markers of severity than increased NTproBNP levels, which is currently considered the strongest predictor of severity, as shown by a study of Vuilleumier *et al* (32). This hypothesis is supported by the fact that only NT-proBNP levels are associated with right ventricular dysfunction on a chest CT scan (32), a factor considered a marker of poor prognosis in PE (41). However, NTproBNP levels are not a suitable decisive marker for thrombolysis (41). NTproBNP and troponin I levels are considered predictors of a poor prognosis in patients with acute PE (42-44).

*NT-proBNP*. In response to left ventricular overload (45) and myocyte stretching (46), an inactive prohormone (proBNP) is synthesized that is cleaved into the active hormone BNP and the inactive N-terminal fragment (NTproBNP) (47,48). BNP is released in response to ventricular strain and is predictive of a negative outcome for patients with PE (49-51). The NTproBNP fraction can also increase in several other disorders including pre-existing left ventricular dysfunction, kidney failure and chronic pulmonary disease, as well as in the elderly (52). Natriuretic peptides are useful prognostic and diagnostic biomarkers in patients with congestive heart failure and, unlike atrial natriuretic peptide, which is primarily produced in the atrial tissue, BNP is primarily produced by the ventricular myocytes and the main stimulus for its production is myocyte stretch (37,48,53,54). Increased serum levels of natriuretic peptides are found in patients with right ventricular pressure overload due to causes other than PE including primary pulmonary hypertension, chronic thromboembolic pulmonary hypertension and chronic pulmonary disease (55-58). NTproBNP can be considered a marker of short-term mortality risk. Additional studies are required to demonstrate whether NTproBNP measurement may play a role in the decision-making for thrombolysis and in identifying patients who could be treated on an outpatient basis (43). In a 2008 study by Klok *et al* (43), it was found that the incidence of right ventricular dysfunction was 45% in patients with elevated NTproBNP levels compared with 4.5% in patients with normal NTproBNP levels (43). NTproBNP measurement in patients with PE is recommended, considering it is a prognostic biomarker (59,60). Data from a study (61) indicate that NTproBNP seems to be the strongest predictor of mortality and hospitalization (for complications such as PE and dyspnea, with or without chest pain) 3 months after the acute event. This biomarker has proven to be the best predictor for identifying low-risk patients when NTproBNP levels are 300 pg/ml (61).

A total of five meta-analyses have investigated the prognostic value of natriuretic peptide measurement in PE, concluding that elevated levels of natriuretic peptides are associated with a poor short-term prognosis (42,43,62-64). An NTproBNP value of 600 ng/l is the threshold for stratifying the risk of death in hemodynamically stable patients with PE (65) and is associated with a poor prognosis in patients with levels NTproBNP >600 ng/l, right ventricular systolic dysfunction and a high PESI score (66-71). Patients with PE and NTproBNP levels <600 ng/l, with absence of right ventricular dysfunction and a PESI score of 0 have a good prognosis (65). A study by Lankeit *et al* (65), consisting of 688 patients, concluded that patients with PE, that were hemodynamically stable but had right ventricular systolic dysfunction and NTproBNP levels >600 ng/l, may benefit from early thrombolytic therapy, as supported by the randomized pulmonary embolism thrombolysis study (65,72), to prevent hemodynamic instability in patients with right ventricular dysfunction and increased NTproBNP levels (65,73). A high mortality rate in PE is associated with NTproBNP levels >600 ng/l, while low NTproBNP levels <600 ng/l are associated with a good prognosis (8). Elevated NTproBNP levels can be used to identify patients at high risk of complications or death but do not justify the initiation of invasive treatments. Normal NTproBNP levels can help identify patients who could be treated on an outpatient basis (43).

*Troponins (cTnT and cTnI)*. Troponin levels increase following myocardial necrosis due to severe pressure overload or prolonged overload on the right ventricle, leading to microscopic myocardial necrosis (45,48). Troponins are sensitive and specific biomarkers for myocardial cell injury, reflecting microscopic myocardial necrosis. In PE, the increase in troponin levels correlates well with the severity of right ventricular dysfunction (33,34,36,74). Serum troponin levels (cTnT >0.07 $\mu$g/l) have a sensitivity of 75% and specificity of 87% in identifying patients at high risk of all-cause mortality. Serum troponin levels (cTnT <0.07 $\mu$g/l) are associated with a good prognosis (8). Patients with elevated serum levels of both biomarkers have a higher short-term mortality risk compared with patients with NTproBNP levels >600 ng/l, but patients with serum levels of cTnT <0.07 $\mu$g/l have an intermediate risk of short-term mortality (8). The best short-term prognosis is seen in patients with NTproBNP levels <600 ng/l and cTnT levels <0.07 $\mu$g/l. Elevated serum levels of troponins and natriuretic peptides can be used to predict patients at high risk of in-hospital death. The primary role of biomarkers is to differentiate between low-risk and intermediate-risk patients (Table II) (8,43,65,75). Elevated levels of troponins and/or BNP in hemodynamically stable patients with PE and right ventricular dysfunction but low risk of bleeding should be considered for thrombolysis, whereas low levels of troponins and natriuretic peptides can be used to identify patients at low risk for complications (76).

*D-dimers*. Studies suggest that the sensitivity and negative predictive value of D-dimers is low in patients with neoplasms (77). A negative D-dimer result cannot safely exclude a diagnosis of PE in patients suspected of PE with a cancer (78); however, other studies have shown that the negative predictive value is comparable to patients without neoplasms (78,79). A study by Di Nisio *et al* (79) suggested measuring D-dimer levels in patients with neoplasms to exclude PE, although these results require confirmation in a larger study (79). The safety and accuracy of a diagnosis based on D-dimer levels in patients with neoplasms have not been established. Neoplasms and their treatment can both reduce accuracy due to an increased likelihood of abnormal results than in patients without neoplasms (80). Reliably excluding PE in patients with neoplasms is of utmost importance as PE is associated with a high mortality rate in these patients and anticoagulant therapy significantly increases the risk of major bleeding (81). D-dimers are not specific for PE. Serum values may also be elevated in other conditions such as myocardial infarction, pneumonia and cancer without PE (80), especially in the elderly, pregnancy, trauma and inflammatory states (82,83). Normal D-dimer levels are more reliable for excluding rather than confirming a diagnosis of PE (82-84). The role of D-dimer measurement in diagnosing PE in patients with clinical suspicion aims to avoid invasive and costly examinations (Table III) (79).

*Electrocardiogram*. Electrocardiographic changes are nonspecific and may suggest small, medium, or large arterial obstruction (Table IV) (85-87).

*Pulse oximetry*. Secondary to PE in the pulmonary arterial bed, there is an imbalance between ventilation and perfusion. $CO_2$ elimination is disrupted, clinically resulting in hypoxia (13).

Table II. Mortality risk in patients with modified biomarkers (8,43,65,75).

| First author/s, year | Studies | NTproBNP >600 ng/l | cTnT >0.07 g/l | Mortality of all cause at 40 days | Mortality with PE patients | Complications | (Refs.) |
|---|---|---|---|---|---|---|---|
| Kostrubiec *et al*, 2005 | 100 patients | - | + | 15% | 8% | - | (8) |
| | | + | + | - | 33% | | |
| | | - | - | - | 3.7% | | |
| Lankeit *et al*, 2014 | 688 patients | + | - | - | 4.2% | - | (65) |
| Klok *et al*, 2008 | meta-analysis of 13 studies | + | - | 10% | - | 23% | (43) |
| Vuilleumier *et al*, 2008 | 146 patients | Hospitalization and death have been evaluated for complications. Result achieved at 12% with NTproBNP being the strongest predictor for command death. | | | | | (75) |

Table III. Importance of D-dimers measurement (79).

| D-dimers | | | | | | | |
|---|---|---|---|---|---|---|---|
| Patients with cancer | | | | Patients without cancer | | | |
| Sensitivity | Specificity | Negative predictive value | Positive predictive value | Sensitivity | Specificity | Negative predictive value | Positive predictive value |
| 100% | 21% | 100% | 31% | 93% | 53% | 97% | 31% |

*Echocardiography*. In patients with PE, echocardiography provides data on right ventricular dysfunction (85) (right ventricular dilation-right ventricular telediastolic diameter >30 mm, right ventricular/left ventricular ratio >1; paradoxical movement of the interventricular septum; presence of a McConnell sign); presence or absence of pulmonary hypertension and presence or absence of clots in the right cavities (13). In acute PE, evidence of systolic pressure in the pulmonary artery >60 mmHg is rarely found; such a value is more indicative of chronic pulmonary hypertension, especially when accompanied by other echocardiographic signs such as right ventricular hypertrophy (13). Increased pressure in the pulmonary artery leads to right ventricular dysfunction and right heart failure, results in the release of cardiac biomarkers such as BNP, NT-proBNP and troponins (13,88). In addition to right ventricular dysfunction and right heart failure, which are the primary causes of death in PE, left ventricular function may also be affected. Left ventricular filling is affected by septal bulging into the left ventricle due to increased volume and pressure in the right ventricle. Diastolic function can also altered. Reduced cardiac output leads to arterial hypotension and shock (13,89). Due to the decrease in left ventricular blood flow, coronary artery blood flow decreases, leading to ischemia and even right ventricular myocardial infarction or mortality in individuals with massive PE, where compensatory mechanisms are overwhelmed and cannot balance oxygen consumption at the myocardial level (13). Echocardiography in acute PE can be used to assist in risk stratification and, using this, patients can be divided into three groups of patients from a prognostic point of view (76): i) No right ventricular dysfunction, in-hospital mortality rate of <4%; ii) sub-massive PE in hemodynamically stable patients with right ventricular dysfunction, in-hospital mortality rate of between 5-10%; iii) severe right ventricular dysfunction and cardiogenic shock, in-hospital mortality up to 30%.

Right ventricular dysfunction diagnosed by echocardiography is a frequent clinical finding in patients with PE and is considered a poor prognostic factor (42,45,49-51,90) and an independent predictor of early mortality in patients with PE (89). Identifying hemodynamically stable patients with right ventricular dysfunction is crucial for initiating therapies such as thrombolysis or embolectomy (91,92), to prevent early hemodynamic deterioration. Echocardiography plays an important role in identifying hemodynamically right ventricle dysfunction (50,93,94) but of significant importance is also computed tomography (CT) angiography, which can be used to predict the risk of complications or death by measuring the ratio between the right ventricle and the left ventricle (41,95-100). However, data from studies evaluating right ventricular dysfunction by CT angiography are limited (101,102).

*Chest X-ray*. The role of chest X-rays is to exclude other acute causes of respiratory failure in patients with suspected PE such as pneumothorax, acute pneumonia, pulmonary edema, tumors, or pleurisy (103).

*CT angiography*. CT angiography is the investigation of choice in patients clinically suspected of PE. Multi-slice CT angiography allows visualization of the arterial tree up to the segmental and subsegmental levels, enabling the diagnosis of

Table IV. Common electrocardiographic changes in patients with pulmonary embolism (86,87).

| Electrocardiographic changes suggestive in PE with small or medium arterial obstruction | Electrocardiographic changes suggestive in PE with large arterial obstruction |
|---|---|
| • Sinus tachycardia | • Right axis deviation<br>• Major or minor right bundle branch block<br>• Q, negative T waves in lead III + negative T waves in V1-V4<br>• Negative T waves in V1-V3<br>• Pulmonary P wave<br>• S1Q3T3 |

even subsegmental pulmonary arterial micro-emboli with a sensitivity of up to 96% (13).

*Lung ventilation-perfusion scintigraphy*. This is a less commonly used diagnostic method for PE compared with CT angiography. In patients with PE, the perfusion scintigram is abnormal, but the ventilation scintigram is normal (13).

*Venous Doppler ultrasound*. Diagnosing DVT in patients with suspected PE allows for the administration of anticoagulant treatment without the need for additional investigations (1). The combination of a negative D-dimer result and negative Doppler ultrasound for DVT safely excludes the diagnosis of PE and can lead to the safe discontinuation of anticoagulant treatment in patients with malignancies (78).

*Pulmonary angiography*. This is the gold standard for diagnosing PE and as it allows for direct visualization of thrombi up to 1-2 mm in size in the pulmonary arteries or their subsegmental branches (1).

*Nuclear magnetic resonance (NMR)*. With reduced availability, NMR is reserved for patients with inferior vena cava thrombosis, iliac vein thrombosis, during pregnancy and for patients with contraindications to contrast agent administration (13).

**3. The anticoagulant treatment dilemma**

Clinically, patients with suspected PE can be classified as high, intermediate, or low risk for early in-hospital or 30-day mortality. Independent predictive factors for mortality include neoplastic conditions, present in 10-20% of patients diagnosed with PE. In ~10% of patients, PE represents the early clinical status before a diagnosis of a malignancy in the 10 years following the acute event; however, most malignancies are diagnosed within 12-24 months following the acute event. Therefore, the European guidelines recommend screening for neoplastic conditions in patients with an apparently unprovoked PE (1). In the absence of hemodynamic instability, signs of right ventricular dysfunction and positive biomarkers, the PESI score can be used to categorize patients with PE as intermediate or low risk. The presence of PE in patients with neoplasms is associated with an increased long-term mortality risk and is considered the second leading cause of mortality (25,85,104). The hemodynamic status of patients with clinically suspected PE plays an important role in the diagnostic and therapeutic strategy. The diagnostic and therapeutic strategy depends on patient risk; for high-risk patients, CT angiography should be performed. If the imaging investigation confirms the presence of a PE, primary reperfusion therapy should be initiated (13). Acute phase treatment of PE aims to alleviate symptoms, limit the progression of thrombosis and prevent death. Long-term treatment aims to prevent recurrent thromboembolic events and chronic thromboembolic pulmonary hypertension (1). Patients at high risk should undergo reperfusion therapy: Thrombolysis, surgical embolectomy, or interventional treatment; along with respiratory and hemodynamic support. Intermediate and low-risk patients should receive anticoagulant treatment (Fig. 1).

For the acute phase treatment patient should be treated as follows: i) Respiratory support, administered to patients with hypoxia including oxygen administration via nasal cannula; ii) hemodynamic support, reserved for hemodynamically unstable patients with hypotension, low cardiac output, or cardiogenic shock; or iii) thrombolytic treatment. reserved for high-risk patients with a Class I indication and Level B evidence and for intermediate-risk or hemodynamically unstable patients with a Class IIa indication and Level B evidence, according to the European Society of Cardiology Guidelines for the Diagnosis and Management of PE (1).

Thrombolytic treatment removes thromboembolic obstruction and, in the short term, it improves right ventricular function and the hemodynamic status. A long-term benefit of thrombolytic treatment is the reduced incidence of chronic thromboembolic pulmonary hypertension (1). Thrombolytic therapy includes recombinant tissue plasminogen activators such as streptokinase and urokinase. Absolute contraindications for thrombolytic therapy are hemorrhagic stroke, ischemic stroke of an unknown etiology in the past 6 months, ischemic stroke in the last 6 months, central nervous system impairment or a cerebral tumor, major trauma, surgery, or cranial trauma in the preceding 3 weeks, gastrointestinal bleeding in the preceding 30 days and a high risk of bleeding. Relative contraindications for thrombolytic therapy include transient ischemic attack in the preceding 6 months, oral anticoagulant treatment, pregnancy, postpartum-first week, puncture in an uncompressible location, trauma resuscitation, uncontrolled hypertension (BP >180 mmHg), advanced liver disease, infectious endocarditis, or an active peptic ulcer (1).

The primary goal of anticoagulant treatment is to prevent the mortality of a patient or the recurrence of PE (105,106).

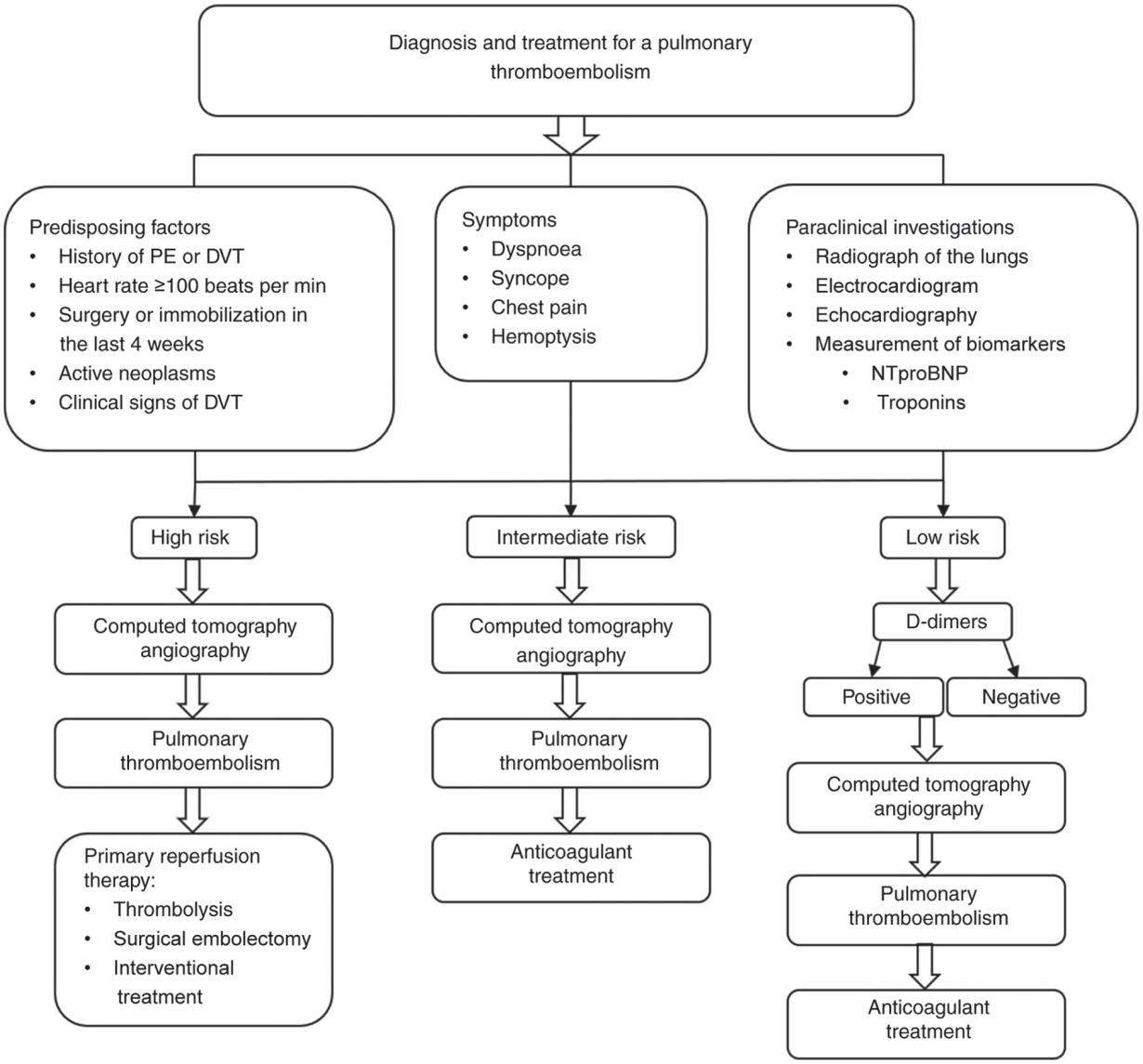


Figure 1. Algorithm for the diagnosis and treatment of PE. PE, pulmonary embolism; DVT, deep venous thrombosis; NTproBNP, natriuretic peptides.

Anticoagulant treatments can be classified as follows: Parenteral administration agents, which include unfractionated heparin (indicated for intermediate-risk patients with signs of hemodynamic instability) (1,103); LMWH (indicated for intermediate or low-risk patients, with a lower risk of bleeding and heparin-induced thrombocytopenia) (13); fondaparinux (low bleeding risk, indicated for intermediate and low-risk patients for 5-10 days); oral anticoagulants; vitamin K antagonists (similar to LMWH regarding mortality and bleeding risk but inferior in recurrent thromboembolic events) (107,108); and novel oral anticoagulants (NOACs; which do not need to be monitored). Certain NOACs (apixaban, rivaroxaban) can be administered immediately after diagnosis without the need for initiation of parenteral anticoagulant.

Surgical pulmonary embolectomy is indicated for patients at high risk of PE where thrombolysis is contraindicated or has failed. It is contraindicated in patients with recurrent pulmonary emboli or severe pulmonary hypertension with suspected chronic thromboembolic pulmonary hypertension (1).

Inferior Cava Vein filters are indicated for patients with recurrent PE secondary to DVT and under effective anticoagulant treatment and for patients with an absolute contraindication to anticoagulant treatment (1,109).

Long-term anticoagulant treatment aims to reduce the number of recurrent thromboembolic events (1). The duration of anticoagulant treatment for patients with 'provoked' or 'unprovoked' PE differs, extending from 3 months in provoked cases to an undetermined period in the case of the second unprovoked embolic episode. This extension requires careful risk/benefit assessment when considering prolonged anticoagulant treatment (1). For patients with recurrent PE and chronic thromboembolic pulmonary hypertension, long-term anticoagulant treatment is recommended indefinitely. For patients with PE and associated neoplastic conditions, initial treatment with LMWH for the first 3-6 months is preferred, given the observed superiority in preventing recurrent thromboembolic events compared with vitamin K antagonists, without being inferior in terms of bleeding risk and mortality.

Continuing anticoagulant treatment beyond 6 months after the acute event is important considering that the risk of recurrence is three times higher in patients with cancer compared with the general population (110,111). Anticoagulant treatment after the acute event should be continued until the neoplastic disease is successfully treated. The decision to continue or discontinue anticoagulant treatment must be made together with the patient, taking into consideration the risk of recurrence, bleeding and the preferences of the patient (1,112). Recurrent thromboembolic events are associated with a significantly higher long-term risk of mortality. Studies (113,114) have suggested that higher doses of LMWH are required for patients with cancer after the second thromboembolic event to lower the mortality rate in these patients (114,115).

NOACs, such as apixaban, rivaroxaban, edoxaban and dabigatran, have been directly compared in a study (115) and the results show a similar efficiency to LMWH regarding the risk of recurrence and the mortality rate. Regarding the safety profile of apixaban and edoxaban, they presented the lowest risk of bleeding (Table V) (114,115).

The use of LMWH is preferable for the long-term treatment of PE associated with cancer; it is unknown whether vitamin K antagonists are superior to NOACs in this category of patients because (Table VI) (114): i) There are no direct comparisons between the different types of NOACs; ii) NOACs have not been directly compared with vitamin K antagonists in a broad spectrum of patients with PE and cancer; and iii) indirect comparisons have not convincingly shown different outcomes between different NOACs.

The Hokusai-VTE study (116) concluded that treating patients with PE and NT-proBNP levels >500 ng/l with edoxaban reduced recurrence of PE compared with patients treated with warfarin. These results suggest that treatment with novel anticoagulants in patients with PE and elevated NT-proBNP is superior to warfarin treatment (65). Assessing the risk of thromboembolic events in hospitalized patients can be achieved using the Padua score, which classifies a patient with a cumulative score of 4 points as at high risk for thromboembolic events (103). Prophylactic treatment of thromboembolic events can be achieved by administering fixed-dose anticoagulants or mechanical methods (103). Routine prophylaxis is recommended in patients with cancer after surgery and for hospitalized patients, but it is not recommended for patients treated on an outpatient basis except if they have multiple myeloma (27,117).

Levine *et al* (117), in a randomized phase II study, compared unfractionated heparin, LMWH and apixaban as the primary treatment for the prevention of venous thromboembolism in patients with a metastatic neoplasm (lung cancer, colon cancer, breast cancer, pancreatic cancer, stomach cancer, bladder cancer, ovarian cancer, prostate cancer, multiple myeloma, lymphomas and cancers of an unspecified primary site) undergoing chemotherapy in the first 6 weeks from chemotherapy initiation with a duration of at least 90 days of chemotherapy. It was concluded that apixaban was well-tolerated in the study population and supported further phase III studies of apixaban for the prevention of venous thromboembolism in patients with cancer receiving chemotherapy (good safety profile, 93.5% risk of bleeding and the risk of major bleeding rate in the apixaban 5 mg group was 2.2%) (117).

Table V. Anticoagulant treatment and class of indication in pulmonary embolism associated with cancer (114).

| Anticoagulants | Class of Indication |
|---|---|
| Low molecular weight heparin | 2B |
| Vitamin K antagonist | 2B |
| Novel oral anticoagulants (apixaban, rivaroxaban, edoxaban and dabigatran) | 2C |

Cohen *et al* (118) evaluated the effectiveness of rivaroxaban (10 mg/day for 35-39 days) with enoxaparin (40 mg/day for 10-14 days) for the primary prevention of PE. It was concluded that the efficacy of standard-duration rivaroxaban was similar to enoxaparin, while the extended-duration rivaroxaban was superior to enoxaparin, but it was also associated with a higher bleeding risk (118) (Table VII).

Anticoagulant treatment in these patients is associated with numerous bleeding-associated complications and the recurrence rate of thromboembolic events should be considered, given it is >3 times higher than in the general population (119). Patients with cancer who develop PE have a reduced life expectancy and the risk of mortality after PE is four times higher compared with patients without cancer (120,121). This can be explained by a more aggressive evolution of the neoplastic process associated with PE (121,122). However, the risk of recurrent PE and death under anticoagulant treatment is reduced from 26 to 2.9% over 36 months (123).

## 4. Conclusions

PE is considered the second leading cause of mortality in patients with neoplastic conditions. Increased NTproBNP levels are associated with acute right ventricular dysfunction. Right ventricular dysfunction diagnosed by echocardiography is a frequent clinical finding in patients with PE and is considered a poor prognostic factor and an independent predictor of early mortality.

In hemodynamically stable patients with PE with elevated troponin and/or BNP levels and evidence of right ventricular dysfunction in the absence of a risk of bleeding, thrombolytic therapy should be considered (76). It is strongly contraindicated in cases of apparent macroscopic bleeding, such as hemoptysis, gross hematuria, or melena and is relatively contraindicated in occult bleeding.

The Hokusai-VTE study (116) concluded that treating patients with PE and NT-proBNP levels >500 ng/l with edoxaban was associated with a reduction in recurrent PE compared with patients treated with warfarin. These results suggest that treatment with new anticoagulants in patients with PE and elevated NT-proBNP levels is superior to warfarin treatment (65).

A negative D-dimer result safely excludes the diagnosis of PE in patients with cancer. The combination of D-dimer measurements with other imaging techniques such as CT or venous ultrasound can improve the diagnosis but requires further investigation (79).

Table VI. Therapeutic strategies in recurrent PE associated with cancer (114)

| Recurrent PE under treatment with: | Consideration for a therapeutic scheme: |
|---|---|
| Vitamin K antagonists (within therapeutic range) | Switch from vitamin K antagonists to full-dose LMWH |
| LMWH | Increase LMWH dose by 25%<br>or<br>introduction of an inferior vena cava filter if the anticoagulant dose cannot be increased (considered as a last resort) |
| Dabigatran | Switch from Dabigatran to full-dose LMWH, at least temporarily (2C) |
| Rivaroxaban | Switch from Rivaroxaban to full-dose LMWH, at least temporarily (2C) |
| Apixaban | Switch from Apixaban to full-dose LMWH, at least temporarily (2C) |
| Edoxaban | Switch from Edoxaban to full-dose LMWH, at least temporarily (2C) |

PE, pulmonary embolism; LMWH, low molecular weight heparin

Table VII. Primary prophylaxis of pulmonary embolism in oncology patients (117,118).

| Anticoagulant | Dose | Duration | Safety profile |
|---|---|---|---|
| Enoxaparin | 40 mg/day | 10-14 days | Good |
| Rivaroxaban | 10 mg/day | 10-14 days | Similar to enoxaparin |
| Rivaroxaban | 10 mg/day | 35-39 days | Superior efficacy to enoxaparin but higher bleeding risk (requires additional studies) |
| Apixaban | 5 mg/day | First 6 weeks from chemotherapy initiation | Good safety profile 93.5%<br>Major bleeding risk 2.2% (requires additional studies) |

Vitamin K antagonists are not considered superior to NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) in the treatment of PE associated with cancer. NOACs have a similar efficacy compared with vitamin K antagonists regarding the risk of recurrence of thromboembolic events and mortality in patients with PE associated with cancer. Edoxaban and apixaban have an improved safety profile, with the lowest risk of bleeding risk in this category of patients (124).

LMWH is preferred in the long-term treatment of PE associated with cancer. In recurrent PE associated with cancer, switching from vitamin K antagonists or NOACs to a full dose of LMWH, at least temporarily (2C level of evidence according to the European Society of Cardiology) (1), or increasing the dose of LMWH by 25% in patients with recurrent PE currently being treated with an LMWH is recommended. Anticoagulant treatment in patients with PE and cancer may be associated with numerous hemorrhagic complications.

The primary role of biomarkers is to differentiate patients at low risk from patients at intermediate mortality risk. NT-proBNP levels in patients with PE are considered a prognostic biomarker. Serum levels of cTnT <0.07 $\mu$g/l is associated with a favorable prognosis. Patients who have elevated serum levels of both biomarkers are associated with a higher risk of short-term mortality compared with patients who have NTproBNP values >600 ng/l but serum levels of cTnT <0.07 $\mu$g/l, which instead have an intermediate short-term mortality risk. Patients with NTproBNP levels <600 ng/l and cTnT levels <0.07 $\mu$g/l have the best short-term prognosis.

Pulmonary angiography is the gold standard in the diagnosis of PE. Prophylactic treatment for PE is routinely recommended for patients with cancer following surgery and for hospitalized patients. The recurrence rate of thromboembolic events in patients with PE associated with cancer is >3 times higher than that in the general population. Patients with cancer who develop a PE have a reduced life expectancy and the risk of mortality after PE is 4 times higher compared with the general population.

The results of the present review could be applied in helping differentiating patients at intermediate risk from patients at low risk of mortality. That could be performed by dosing biomarkers that are considered short-term prognostic markers and by imaging studies (echocardiography and CT angiography to identify right ventricular dysfunction) and thus to prevent early hemodynamic deterioration that correlates with increased mortality by initiating thrombolytic/anticoagulant therapy as soon as possible. On the other hand, the present review wants to shed light on the fact that in neoplastic patients, although they have an increased risk of thromboembolic events and the risk of bleeding associated with anticoagulant treatment is not negligible, the prevention of thromboembolic events in the first 12 months of neoplasia diagnosis may markedly reduce the risk of mortality in these patients.

The present review tried to increase the interest in new research studies, originals or meta-analyses, performed on

cohorts of cancer patients, studies that have to compare the effectiveness in preventing and treating thromboembolic events and safety profiles of different NOACs, of NOACs compared with LMWH and antivitamins K. These research studies will have to address the mortality, the recurrence of thromboembolic events as well as the risk of bleeding in order to identify the classes of anticoagulants with the lowest risk of bleeding and the maximum prophylactic effect on thromboembolic events. Currently, there are no direct studies to compare different NOACs in terms of effectiveness and safety profile in cancer patients.

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DMN conceived the topic and wrote this scientific work. CAP and RU reviewed and edited the manuscript. RMR and AGR revised the content of this article. All authors read and approved the final manuscript. Data authentication is not applicable.

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The authors declare that they have no competing interests.

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