Cardiology Lab Essentials
Chapter 5

LAB MARKERS IN PULMONARY EMBOLISM

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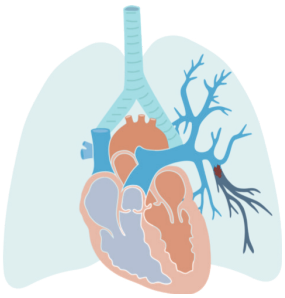
REVIEWING PULMONARY EMBOLISM

Most pulmonary embolisms originate from thrombi in the deep venous system, mostly from proximal veins of the lower extremities.

Features of pulmonary embolism



The thrombus obstructs the pulmonary artery or one of its branches and pulmonary artery resistance increases, leading to pulmonary hypertension and an increased right ventricular afterload. The right ventricle has a hard time working against this pressure. Eventually the right ventricular output drops, which can lead to right ventricular failure.

The drop in right ventricular output leads to an impaired left ventricular filling and thus a decreased left ventricular cardiac output, which in turn causes a fall in blood pressure.

Another feature of pulmonary embolism is respiratory failure. This is partly due to desaturation of mixed venous blood resulting from the decreased cardiac output, and partly due to ventilation-perfusion mismatch in the pulmonary vessels.

Severity of pulmonary embolism

- Acute: presenting immediately after obstruction of the pulmonary arteries.
- Subacute: occurring days or weeks later.
- Chronic: with pulmonary hypertension developing years later.

Symptoms

Symptoms of pulmonary embolism are non-specific.

Most common symptoms, according to their frequency

- Dyspnea
- Chest pain, classically pleuritic
- Coughing
- Symptoms of deep vein thrombosis (calf or thigh pain and swelling)

Less common symptoms

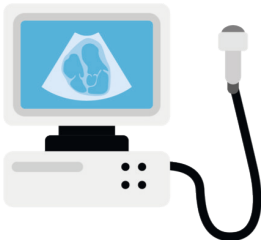
- Fever
- Hemoptysis
- Arrhythmias
- Syncope

In diagnostics, it is helpful to distinguish between hemodynamically stable and hemodynamically unstable presentation. Hemodynamically unstable pulmonary embolism is characterized by persistent arterial hypotension and is associated with a greater risk of death within the first hours to days.

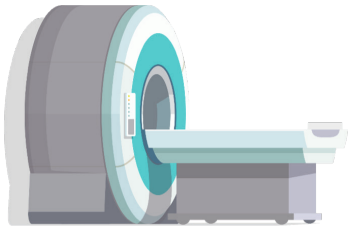
Diagnostic steps

1. Medical history and physical exam

2. Risk assessment score



3. Labs and / or imaging studies

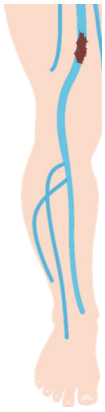


4. Computed tomography (CT) angiography to confirm the diagnosis

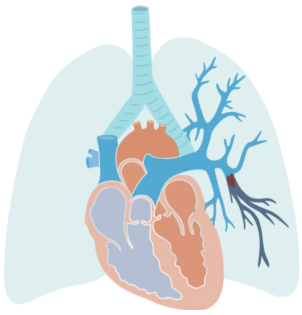
UNDERSTANDING D-DIMER TESTING

Coagulation and fibrinolysis both occur in thromboembolism. D-dimers are fibrin degradation products and therefore their presence indicates fibrinolysis.

D-dimers are important lab markers in all kinds of thromboembolism, including

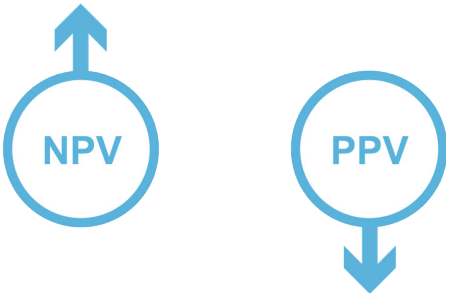


Deep vein thrombosis



Pulmonary embolism

D-dimer tests are very sensitive, but not very specific. The negative predictive value to diagnose thromboembolism is very high, the positive predictive value, on the other hand, is fairly low.



Consequently, if a patient's test result is negative, you can be almost 100% certain that they do not have a thromboembolism, provided the pre-test probability is not high.

Thus, D-dimer testing is ideal to rule out any kind of thromboembolism, such as pulmonary embolism. On the other hand, it is rather weak at ruling in.

Age-adjusted cutoff level

The common cutoff level for D-dimer in adults is 500 ug / L.

In patients over the age of 50, the use of age-adjusted cutoff levels is recommended. To obtain the new cutoff, multiply the age of your patient by ten.

Age x 10 µg / L

Other causes for D-dimer elevations

Causes other than thromboembolism that account for D-dimer elevations

- Pregnancy
- Malignancy
- Trauma
- Surgery in the last four weeks
- Inflammatory processes
- Disseminated intravascular coagulation (DIC)
- Severe liver cirrhosis
- Severe kidney failure

GETTING TO KNOW THE DIAGNOSTIC TOOLS

When pulmonary embolism is suspected, it is important to obtain a thorough physical exam and medical history from the patient, as a first step in the diagnostic workup. The next step is to use pre-test assessment tools to decide how to proceed further.

Pre-test assessments

Pre-test assessments are tests that help to establish the pre-test probability—that is, the probability that your patient actually has the disease you plan to test them for. These tests increase the specificity, and thus the positive predictive value, of the lab and imaging tests chosen thereafter.

The two most commonly used pre-test assessments

- The WELLS criteria for pulmonary embolism
- The revised GENEVA score

Both are based on a combination of clinical history, vital signs and symptoms. There are two- and three-level models available. The following details refer to the three-level model. These pre-test clinical assessments will classify a patient's risk of having a pulmonary embolism as **high**, **moderate** or **low**.

The following variables are used to calculate the WELLS criteria for pulmonary embolism

- Clinical signs and symptoms of deep vein thrombosis
- Pulmonary embolism is the most likely diagnosis
- Heart rate
- Immobilization for at least three days or surgery in the previous four weeks
- Hemoptysis
- Malignancy, with treatment within six months or palliative
- History of deep vein thrombosis or pulmonary embolism

The following variables are used to calculate the revised GENEVA score

- Age
- Previous deep vein thrombosis or pulmonary embolism
- Surgery or lower limb fracture in the past month
- Malignancy, currently active or cured within the last year
- Unilateral limb pain
- Pain on limb palpitation
- Hemoptysis
- Heart rate

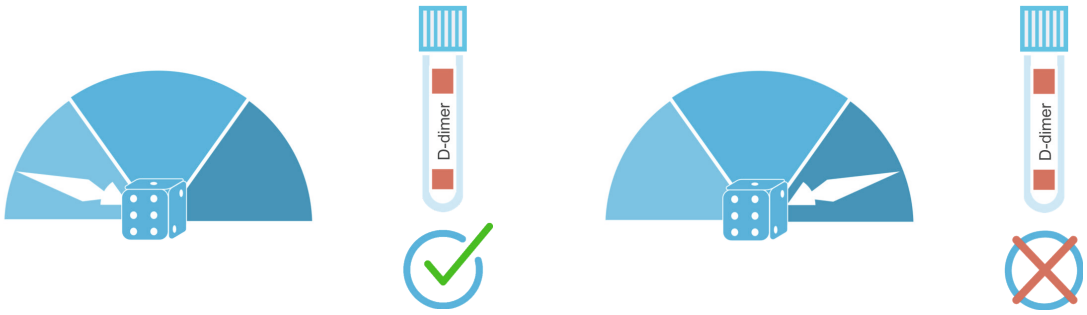
There are online calculators and mobile apps to help you calculate and interpret your patient's risk. Both assessment tests have recently been simplified in order to increase their clinical practicability.

If the patient has a low probability of having a pulmonary embolism according to the WELLS criteria, the Pulmonary embolism rule-out criteria (PERC) can help to determine whether or not further testing is necessary.

D-dimer testing

D-dimer testing shows a very high negative predictive value. Consequently, it is very good at ruling out thromboembolism, such as pulmonary embolism.

D-dimers testing is very useful in patients with a low or moderate pre-test probability—as shown by the WELLS or the revised GENEVA score. In patients with a high pre-test probability, D-dimer test results do not provide any helpful additional information.



Imaging studies

The best imaging technique to diagnose pulmonary embolism is computed tomographic (CT) pulmonary angiography.

Other imaging techniques that are suitable for diagnosing pulmonary embolism include ventilation / perfusion scintigraphy, compression venous ultrasonography, and echocardiography.

DIAGNOSING PULMONARY EMBOLISM

Every diagnostic path starts with talking to the patient, recognizing symptoms, asking the right questions, and examining thoroughly. If you then suspect pulmonary embolism, the next step is to conduct a risk assessment. You can use the WELLS criteria or the revised GENEVA score to establish the patient's probability of having pulmonary embolism. Depending on the clinical probability, you can then either order labs first or conduct imaging studies right away.

High probability

If the risk assessment tools suggest the patient has a high probability of having a pulmonary embolism, you need to determine whether the patient is hemodynamically stable or unstable.

Hemodynamically unstable patients must proceed immediately to a CT angiography, if available. If CT angiography is not available, then echocardiography is recommended as the next best diagnostic step to evaluate the right ventricle and look for differential diagnosis.

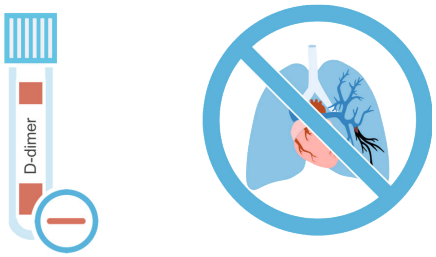
In **hemodynamically stable** patients, imaging studies such as a CT angiography, lung scintigraphy or a compression venous ultrasound should be ordered. The imaging test used will be based on the patient's clinical situation and medical history and, often, by the availability of the test in your institution.

D-dimer testing is not recommended in patients with a high probability of having pulmonary embolism.

Moderate / low probability

If the risk assessment indicates the patient's probability of having pulmonary embolism is moderate or low, the next step is to test for D-dimers.

If the D-dimer result is below an age-adjusted cutoff level, the diagnosis of pulmonary embolism can be ruled out due to the test's high negative predictive value. You should then consider differentials or you might even be able to discharge your patient.



If the D-dimer result is above an age-adjusted cutoff level, then you need to continue with imaging studies.

Pulmonary embolism rule-out criteria (PERC)

The pulmonary embolism rule-out criteria (PERC) should be used in dyspneic patients with suspected pulmonary embolism, who present to the emergency department and have a low probability of having pulmonary embolism, according to the three-level WELLS criteria. PERC helps the clinician to decide whether a patient needs further workup or not.

The following variables are used to evaluate for PERC

- Age
- Heart rate
- Oxygen saturation on room air
- Unilateral leg swelling
- Hemoptysis
- Recent surgery or trauma within the past four weeks requiring treatment with general anesthesia
- Prior pulmonary embolism or deep vein thrombosis
- Hormone use (oral contraceptive, hormone replacement therapy, estrogenic hormone therapy)

If none of the eight PERC criteria are met, the chance that the patient has a pulmonary embolism are < 2% and pulmonary embolism can be ruled out right away, even without D-dimer testing.

If one or more PERC criteria are met, pulmonary embolism cannot be ruled out and further workup is necessary.

GUIDING THERAPY USING LAB MARKERS

Many different treatment options are available for pulmonary embolism. From the most aggressive to the least aggressive option, these include

- Thrombolytic therapy
- Surgical or catheter embolectomy
- Anticoagulation with hospitalization
- Anticoagulation with early discharge
- At-home treatment

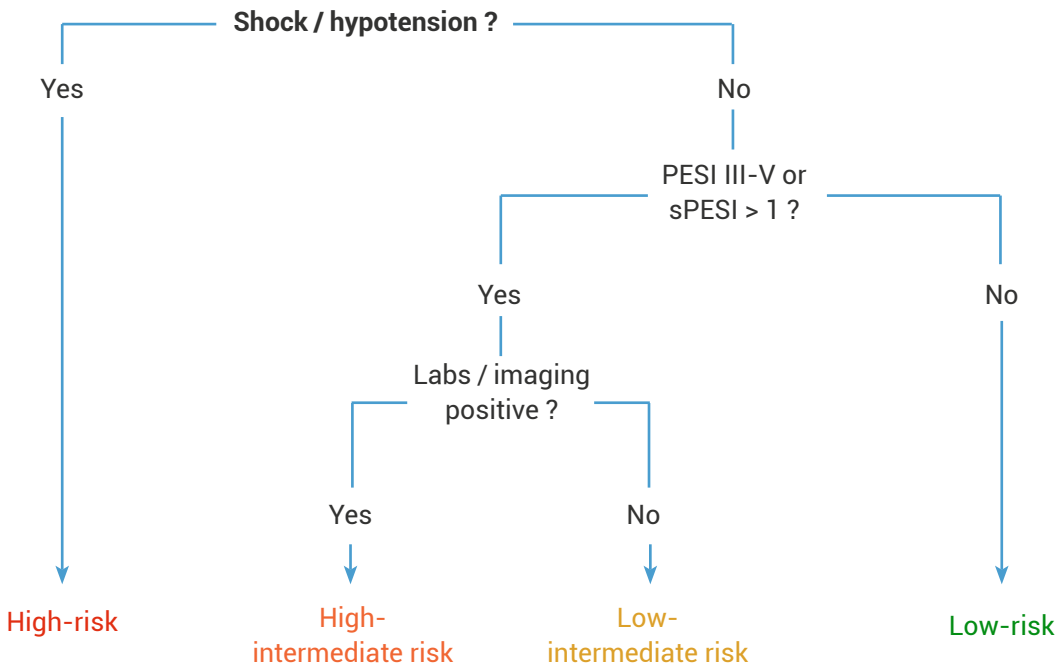
Acute risk stratification

Acute risk stratification can be used to choose the right treatment option. The higher the patient's risk of 30-day mortality due to right ventricle dysfunction, the more aggressive the treatment should be.

Risk is stratified upon four factors

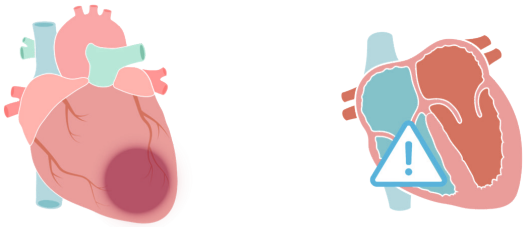
1. Hemodynamic stability
2. The Pulmonary Embolism Severity Index (PESI) score
3. Imaging parameters of right ventricular dysfunction seen on echocardiography or computed tomography of the heart
4. Labs for myocardial damage and / or right ventricular dysfunction

Risk stratification flow chart



Lab markers in risk stratification

Lab markers can help to evaluate myocardial damage and right ventricular function.



There are three markers recommended in recent guidelines

- Troponin
- BNP / NT-proBNP
- Heart-type fatty acid binding protein (H-FABP)

The most sensitive marker to show myocardial damage is **troponin**.

The most sensitive marker to detect ventricular dysfunction is **B-type natriuretic peptide (BNP)**.
In the lab we can measure either the bioactive BNP or a non-active N-terminal fragment of a BNP precursor, called NT-proBNP.

Heart-type fatty acid binding protein (H-FABP) is a cytoplasmic protein that is released from myocytes upon myocardial damage. In the future it might be used, along with troponin and BNP, to evaluate myocardial damage; however, it is a rather young biomarker in this context and larger studies are needed to confirm it's usefulness before H-FABP becomes a routine marker in this situation.

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