

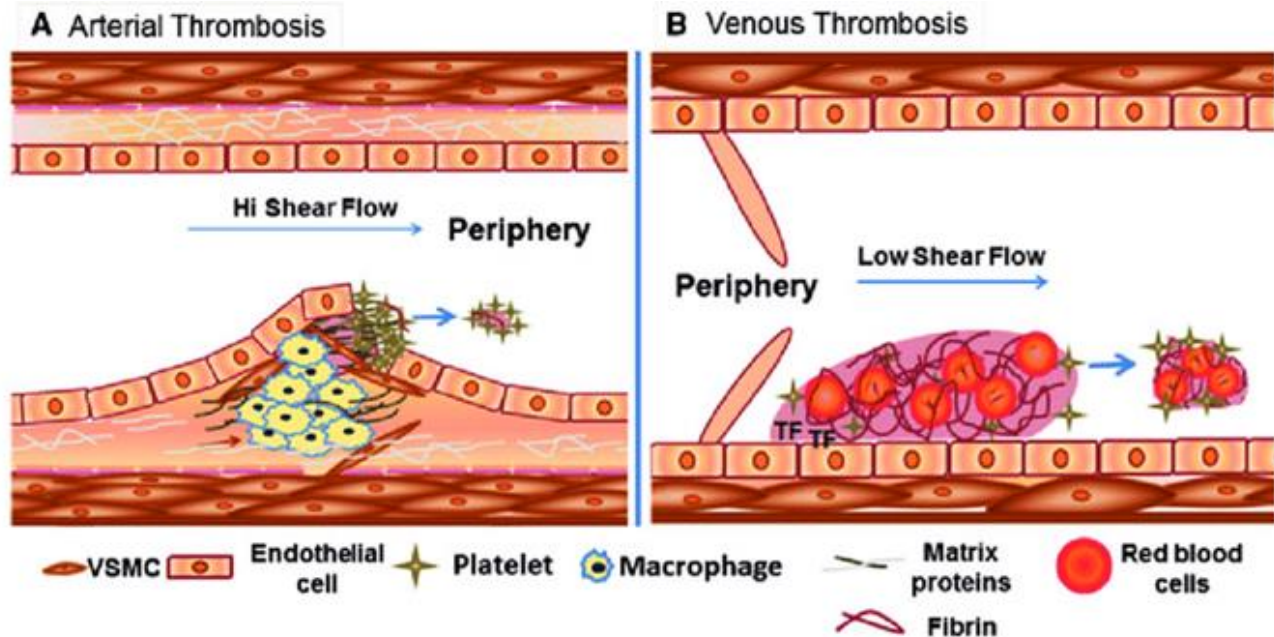


International Registry for Cancer and Thrombosis - RIETE trial

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High School Scholars Day
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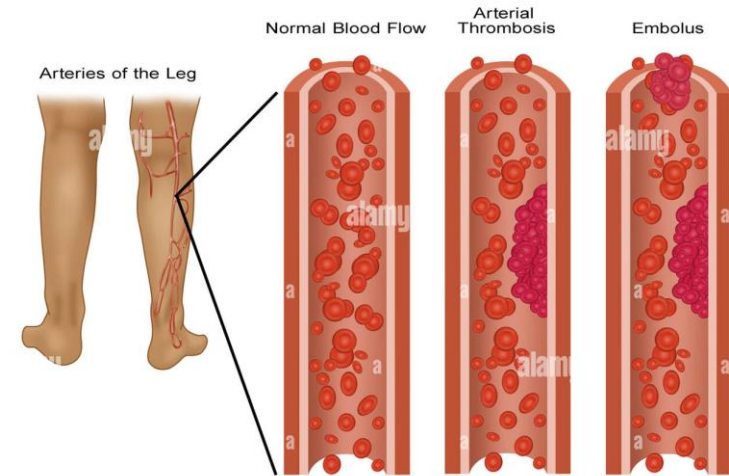
Thromboembolism

Blockage of a blood vessel by a blood clot that has become dislodged from its original position



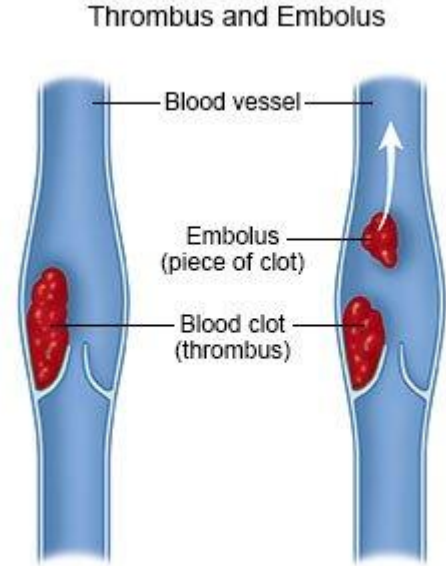
Arterial Thromboembolism (ATE)

- The clots that get stuck inside arteries can block blood flow and deprive the the tissues of oxygen and blood which causes necrosis (tissue death)
- Site of ATE
 - Arterial thromboembolism often occurs in the legs and feet
 - Occuring in the brain can cause stroke
 - Occuring in the heart can cause a heart attack
- Risk factors
 - Atrial fibrillation, injury to the artery wall, smoking, sedentary lifestyle, diabetes, obesity, high cholesterol levels, high blood pressure, etc.
- Treatment
 - Anticoagulants (heparin, warfarin, etc.)
 - Antiplatelet medicines (aspirin) to prevent further blood clots from forming
 - Surgery (embolectomy, angioplasty, arterial bypass)



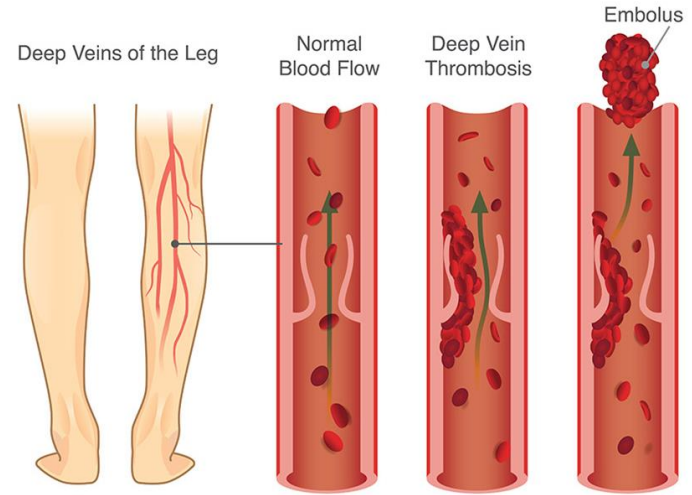
Venous Thromboembolism (VTE)

- A blood clot is dislodged and blocks a vein
- Types of VTE
 - DVT: Occurs when a blood clot forms in the deep veins which are usually located in the lower leg, thigh, or pelvis
 - Symptoms of DVT include swelling, pain, and redness
 - PE: Occurs when a blood clot breaks off and travels to the lungs which can cause chest pain and shortness of breath
- Risks of developing VTE include major surgery, inflammation, infection, family history, chronic illnesses such as cancer and heart diseases, smoking, obesity, sedentary lifestyle, age, oral contraceptives, etc.



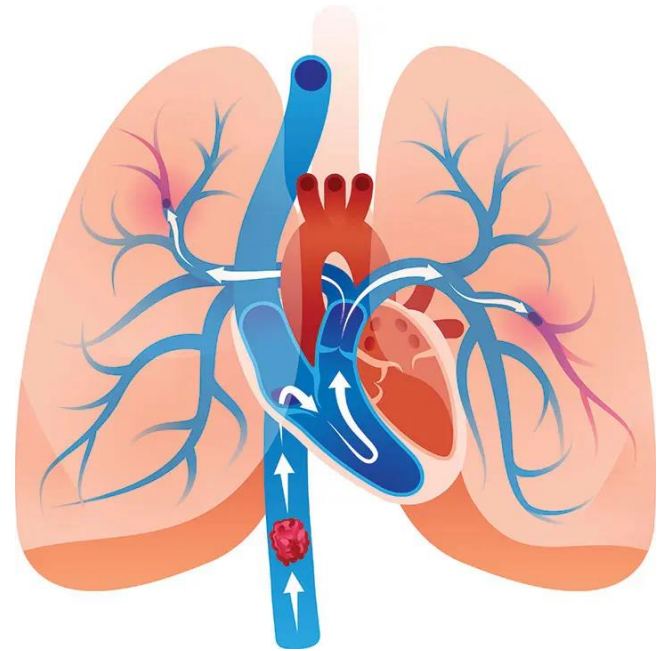
Deep Vein Thrombosis (DVT)

- Occurs when a blood clot forms in the deep veins which are located in the lower legs, thighs, and pelvis called lower extremity DVT. Although much less common, DVT can also occur in the arms
- Symptoms
 - Swelling, redness, discoloration, pain, cramping, tenderness
- Diagnosis
 - Blood tests to determine if the patient has elevated D-dimer levels
 - CT or MRI scans
- Treatment
 - Blood thinners: These allow blood to flow around the blood clot and keep the blood clot from moving which can reduce the chance of PE. Blood thinners do not directly remove the clot.
 - Surgery: DVT Thrombolysis (Inserting a small catheter into the leg), angioplasty (widening the vein through a stent)



Pulmonary Embolism (PE)

- Occurs when a blood clot travels to the lungs: The parts of the lungs that receive blood from arteries do not get enough blood and start to die with PE which is known as a pulmonary infarction. This makes it much harder for the lungs to function properly and provide oxygen to the rest of the body.
- Symptoms
 - Shortness of breath
 - Chest pain (Sharp chest pain can be felt when trying to take deep breaths and can also occur when coughing and bending over)
 - Fainting
 - Coughing up blood
 - Irregular heartbeat (arrhythmia)
 - Lightheadedness
- Manifestation
 - PE can lead to pulmonary hypertension (high blood pressure in the lungs and right side of the heart)
 - The blood clots restrict blood flow which causes the heart to increase its force causing the high pressure

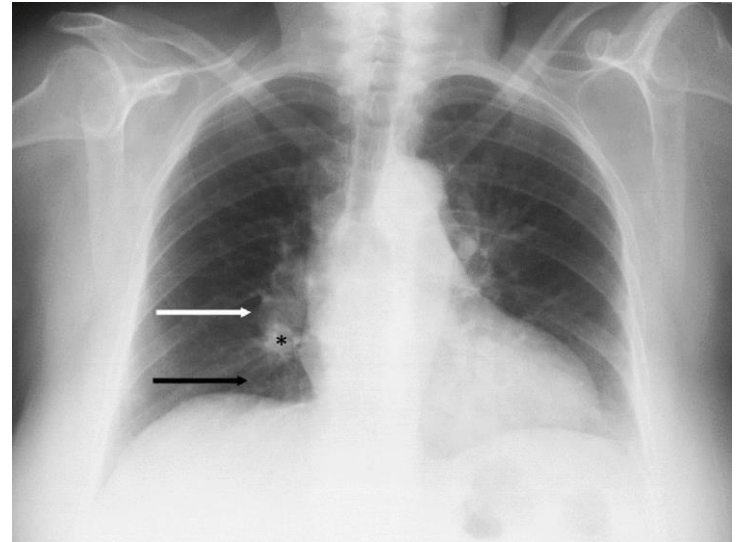


Pulmonary Embolism (PE) cont.

Diagnosis of PE:

- Chest X-ray
 - They can reveal information about other factors such as fluid in the lungs which can help to rule out what is not causing the symptoms the patient is experiencing
- V/Q Scan (Ventilation-perfusion scan)
 - This scan examines the movement of air and blood within the bronchi and lungs respectively
 - Mismatched perfusion defects may indicate PE
- Pulmonary Angiogram
 - X-ray of blood vessels
- CT Scan

Central PE Detected on a Chest X-Ray



Registries Available on VTE

- RIETE Registry
- TROLL Registry
- Garfield VTE Registry (Global Anticoagulant Registry in the FIELD)
- Cancer VTE Registry
- PREFER in VTE Registry
- SWISS Venous ThromboEmbolism Registry (SWIVTER)
- VTEval registry



RIETE Registry

- The registry started collecting data in Spain in 2001
 - Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Belgium, Czech Republic, Republic of Macedonia, Greece, Canada, Brazil, United States, Argentina, and Ecuador
- In contrast to other randomized trials with clinical intervention, these trials followed the management of VTE given by the patient population's physicians (no standardization of treatment)
- The aim of this registry was to improve the treatment of VTE determined through the following factors:
 - Patient demographics, management, and in-hospital and post-discharge results



RIETE Registry

- The population of this registry included patients with acute DVT or PE
 - Currently includes 124,602 patients
 - Of the 13,011 patients enrolled in 2005 22% were aged greater than 80 years.
 - Of the 14,391 patients enrolled in 2006 20% had active cancer
- Exclusion criteria includes the patients participating in another therapeutic trial where the patients did not know information about their treatment (blind medication)
- Follow Up
 - 10,000 patients had a follow up at 1 year and 5,000 patients had a follow up at 2 years



TROLL Registry (Venous Thrombosis Registry in Østfold Hospital)

- Norwegian Registry
- The aim of this registry was also to include different groups that had been excluded from previous registries
- This registry has been collecting data since 2005 of patients who were 18 years of age and above who were diagnosed, treated, and had a follow up about their condition
- The registry had more than 5000 patients with VTE
- Their patient population consisted of mostly patients from 55-77 years of age where 52.1% of the population were male
 - In the male patient population most experienced PE (54.3%) or DVT (40.4%) and a smaller percentage (5.3%) had upper-extremity DVT or splanchnic or cerebral sinus vein thrombosis
 - 46.3% had unprovoked DVT and 22.5% had cancer
 - The most common treatments were DOAC's, LMWH, and vitamin K antagonists
 - They saw an increase in outpatient treatment from 3% to 23%



GARFIELD VTE Registry (Global Anticoagulant Registry in the FIELD)

- Global registry including 10,000 patients who are being treated for VTE from 28 different countries where patients were followed for 3 years
- The goal of this registry was to determine the variations in local treatment around the world and evaluate how these variations affected clinical and economic outcomes
- Some of the countries included were the U.S., China, Australia, and Turkey



Cancer VTE Registry

- Patients with colorectal, lung, stomach, pancreatic, breast, or gynecologic cancer before starting cancer treatment in Japanese patients
- 9630 patients aged 20 years or older
- Their aim was to create a registry that included the East Asian population
- Investigated how cancer type, stage of cancer, and incidence of VTE affected outcomes during the follow-up period
- Pancreatic cancer patients had the highest incidence of VTE (8.5%)
- Breast cancer patients had the lowest incidence of VTE (2.0%)

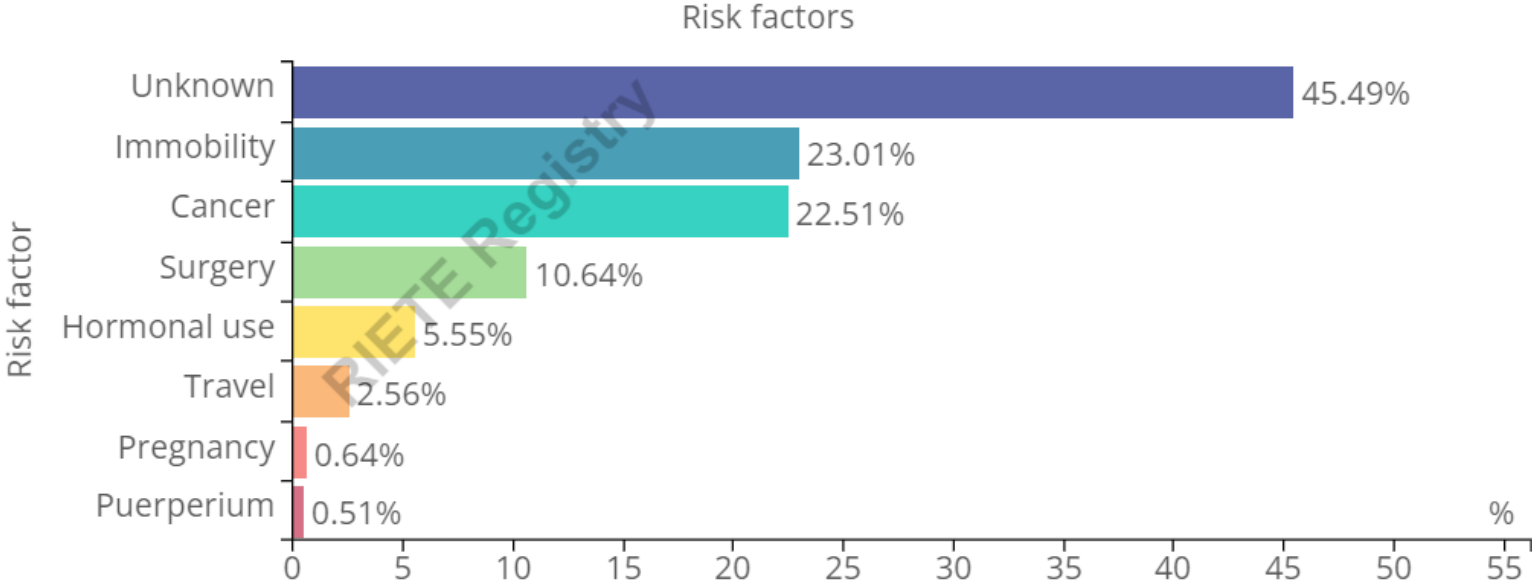


PREFER in VTE Registry

- Included 7 European countries
 - Austria, France, Germany, Italy, Spain, Switzerland, and the UK
- 3545 patients were enrolled in this registry in one year
- The purpose of this registry was to determine factors (quality of life, patient satisfaction, etc.) in order to understand different methods of medical care and identify areas of improvement
 - Estimated costs for a 12-month period of treatment

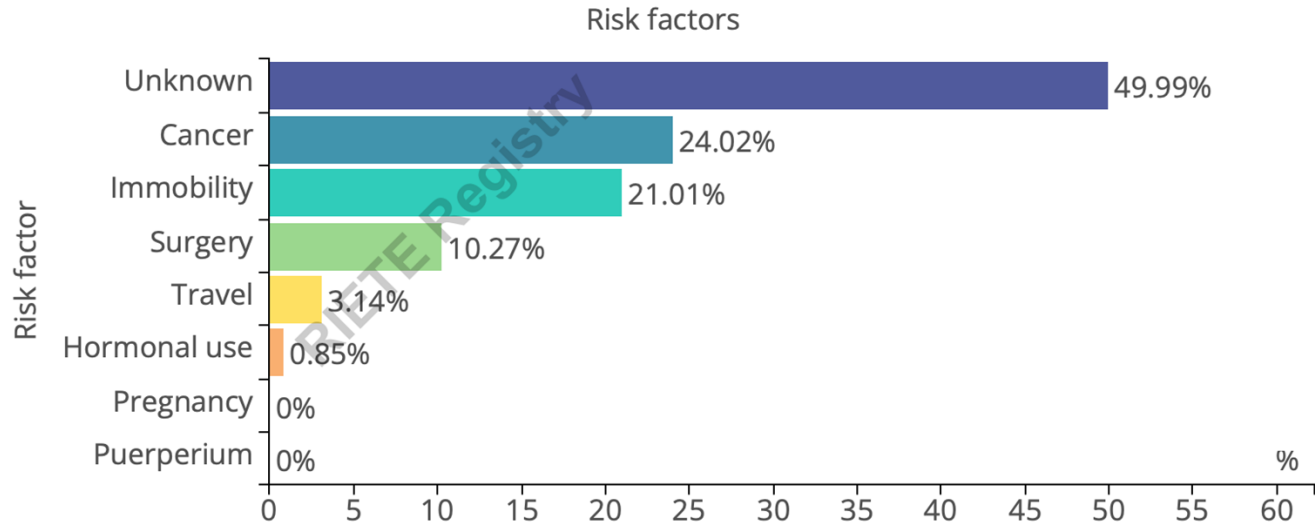


Risk Factors for VTE:

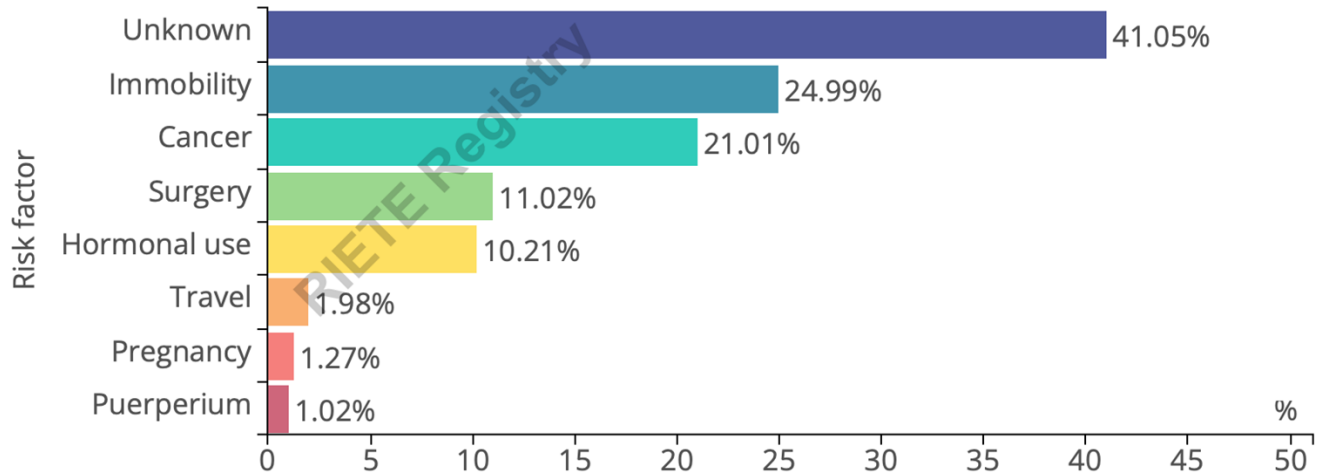


Risk Factors for VTE:

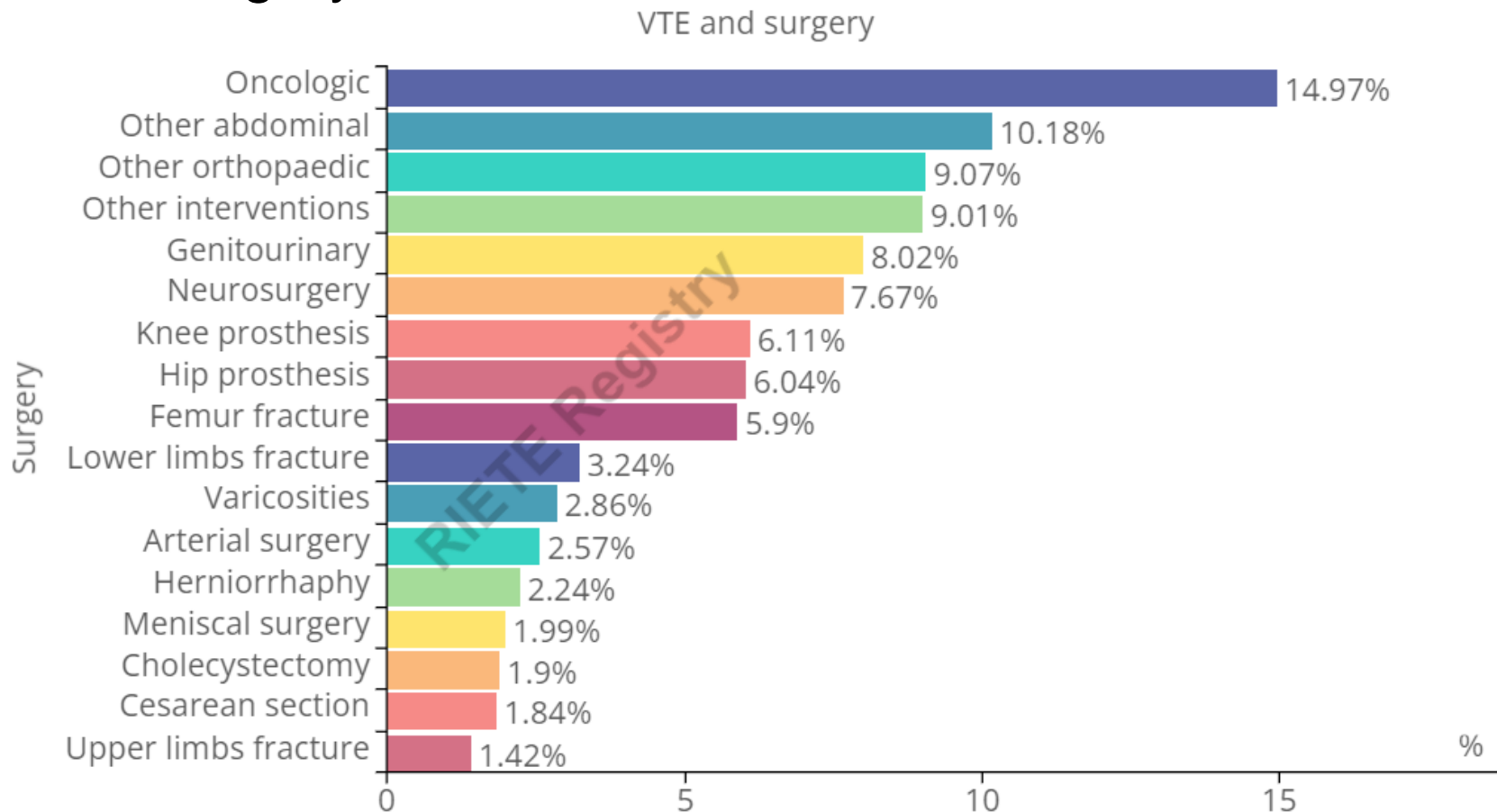
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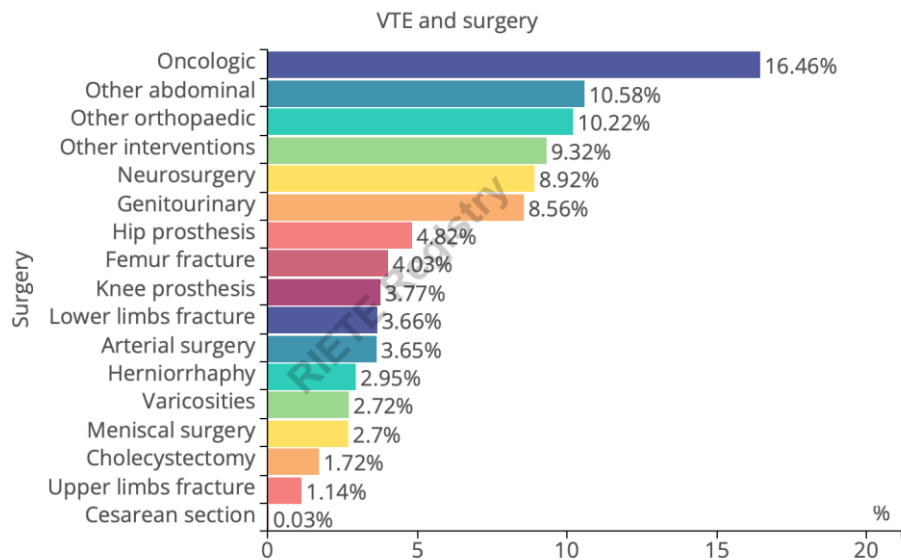


VTE and Surgery

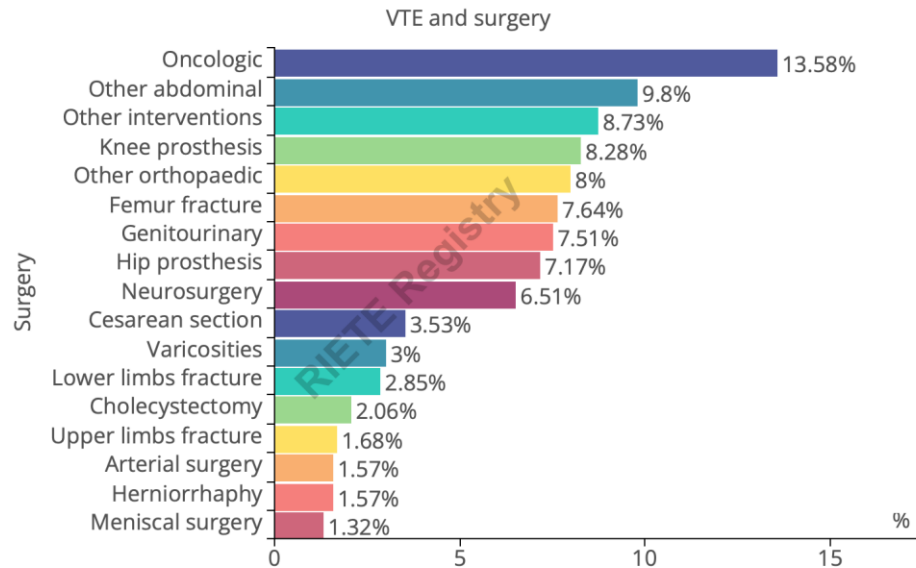


VTE and Surgery

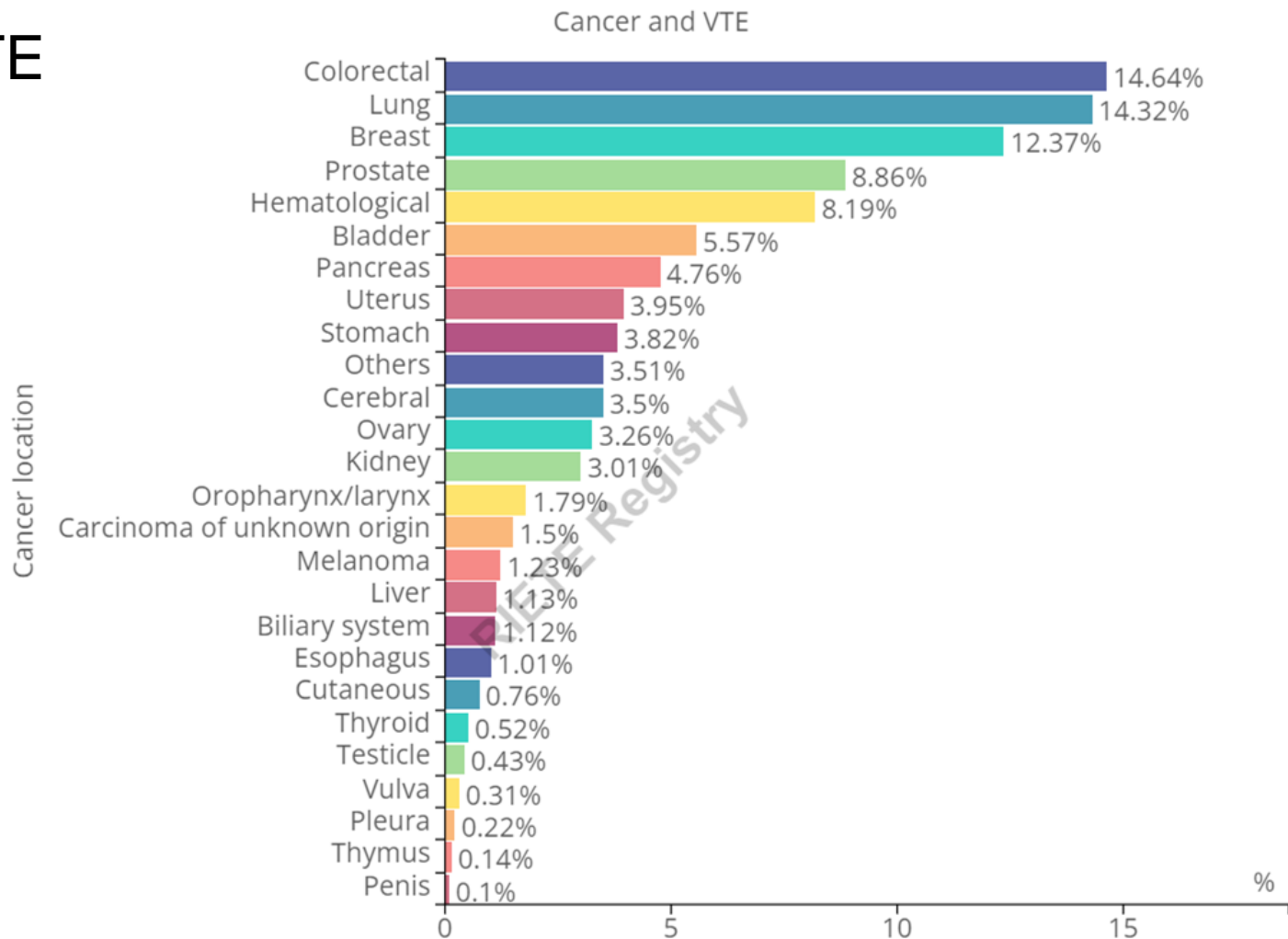
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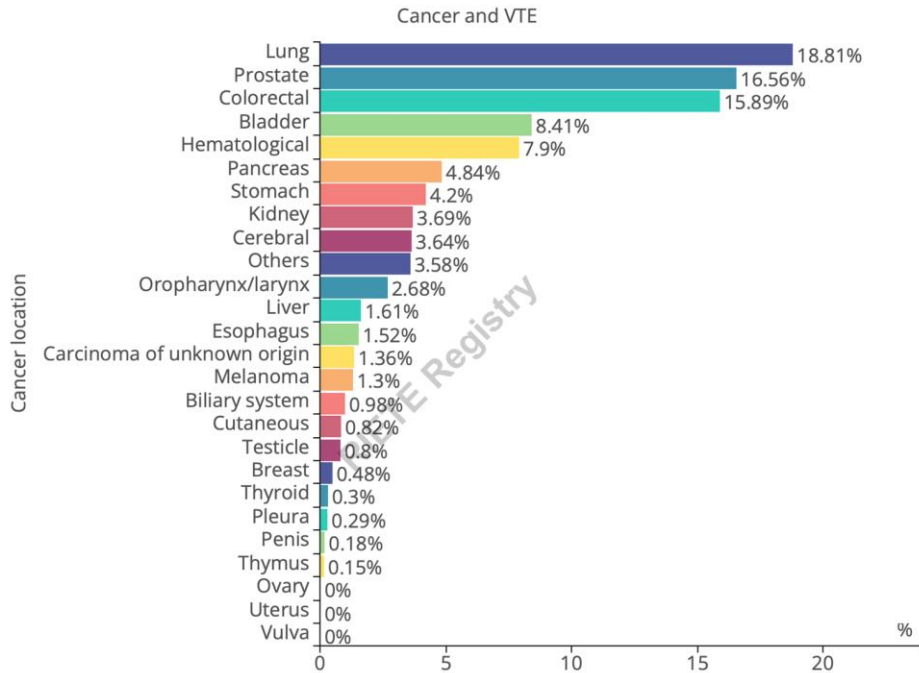


Cancer and VTE

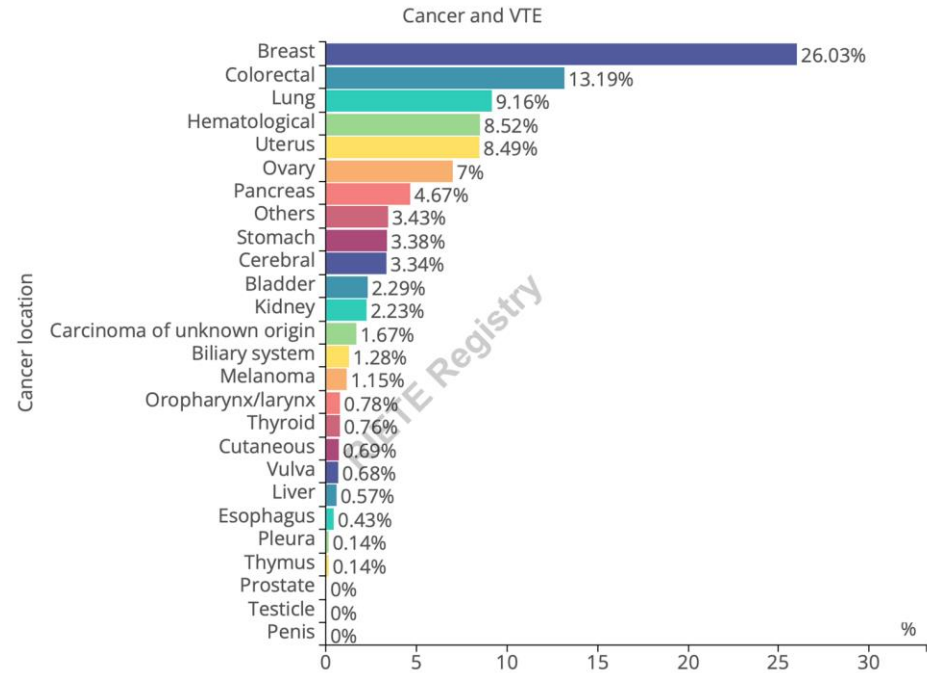


Cancer and VTE

Male:



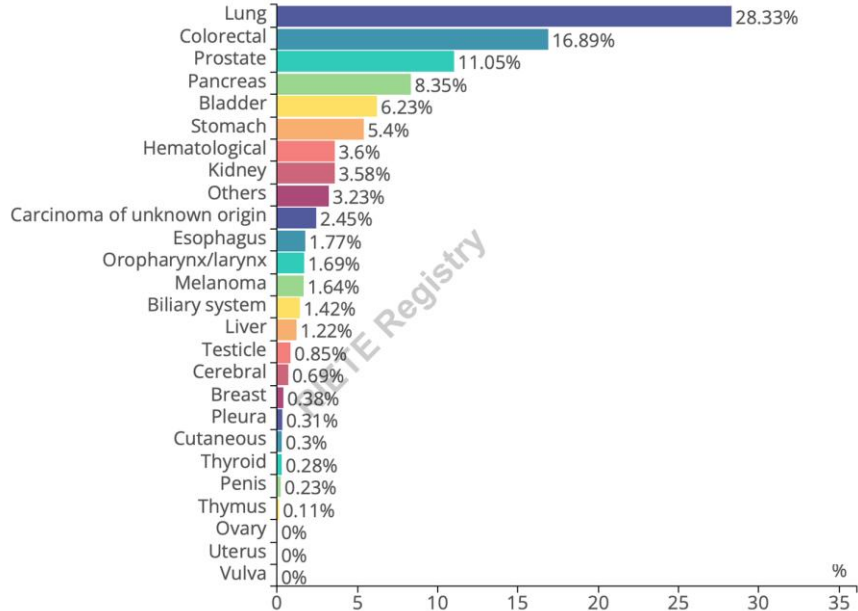
Female:



Cancer and VTE: Metastasis

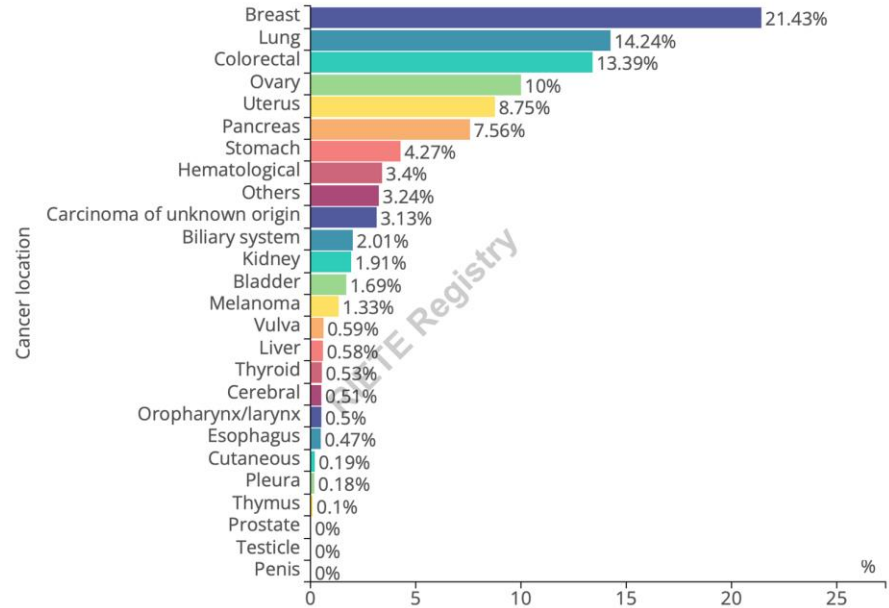
Male:

Cancer and VTE



Female:

Cancer and VTE



RIETE Trials- Conclusions/Findings

- 26% of patients who had VTE in the population also had at least one exclusion criteria yet they had a 4x higher chance of fatal PE or fatal bleeding than in patients without exclusion criteria
- During the first 3 months of therapy 3.4% of patients >80 years and 2.1% of patients <80 years experienced major bleeding
 - Fatal bleeding occurred in 0.8% and 0.4% in these groups
- Fatal PE was more common in patients with recent immobility
- Age was associated with an increased risk of fatal bleeding within the first 3 months
 - With every increase of 10 years of age, the ratio of fatal bleeding increased by 1.37
- Rates of fatal PE or bleeding in cancer patients was significantly higher than that of patients without cancer
 - From the 2006 cancer population the rate of fatal PE was 2.6% and the rate of fatal bleeding was 1.0%
- Patients with an elevated WBC count were at increased risk of recurrence of VTE, fatal bleeding, and death
- Weight
 - Patients weighing <50 kg had a much higher rate of bleeding complications

RIETE Trials- Conclusions/Findings cont.

Risk factors of VTE:

- In 50% of the patients from this study, the causes of VTE were unknown
- For patients who did have an identifiable cause the following were the most common: immobility, cancer, surgery, hormonal use, travel, and pregnancy

Surgery and VTE

- The most common surgeries patients had leading to their diagnosis of VTE were oncologic, abdominal, orthopaedic, etc.

Cancer and VTE

- Around 1 in every 10-20 patients with cancer will develop some form of VTE
- The most common types of cancer in the patient population included colorectal, lung, breast, and prostate cancer

Outcomes:

- Major bleeding and VTE recurrence both increase at around the same rate
- DVT and PE recurrence also have similar rates

RIETE Registry Bleeding

Anemia (Hb < 13 [men] or 12 [women] g/dL)	1.5
Cancer	1
Clinically overt PE	1
Age >75 years	1
Total	8

Results

- Low-risk 0.0
- Intermediate-risk, ≥ 1
- High-risk, ≥ 4

Major Bleeding:

- The average blood volume is 4.5-5.5 liters
- Losing 20% of their blood volume without treatment puts the patient at risk of death

RIETE Score for Fatal Bleeding

Fatal Bleeding

- Bleeding as the cause of death within 7 days
- The average blood volume is 4.5-5.5 liters
- Losing 40-50% of their blood volume without treatment puts the patient at risk of death

Results

- Low-risk, <1.5
- Intermediate-risk, 1.5-4
- High-risk, > 4

RIETE score for fatal bleeding in patients receiving anticoagulation for acute venous thromboembolism [14].

	Points
Age >75 years	1
Metastatic cancer	2
Immobility ≥ 4 days*	1
Recent major bleeding [#]	1.5
Abnormal prothrombin time	1
CrCl < 30 ml/min	1
Platelet Count < $100 \times 10^9/L$	1
Anemia [†]	1
Distal DVT	-1

PESI and sPESI Score

- Predicts the 30-day mortality/outcome in patients with PE
- The RIETE results were used to validate and simplify the PESI score to help create the sPESI score
- The accuracy of the PESI and sPESI scores were not different using RIETE data

Original and Simplified Pulmonary Embolism Severity Index (PESI)		
Variable	Score	
	Original PESI	Simplified PESI
Age	Age in years	Age \geq 80 = 1
Male sex	+10	
History of cancer	+30	1
History of heart failure*	+10	1*
History of chronic lung disease*	+10	1*
Pulse \geq 110 beats/min	+20	1
Systolic blood pressure < 100 mm Hg	+30	1
Respiratory rate \geq 30 breaths/min	+20	
Temperature < 36°C	+20	
Altered mental status	+60	
Oxygenation saturation < 90%	+20	1
PESI Score		
Score	Class	30 day mortality
< 65	I	0-1.6%
66-85	II	1.7%-3.5%
86-105	III	3.2%-7.1%
106-125	IV	4.0%-11.4%
> 125	V	10.0%-24.5%
		SPESI – \geq 1 point warrants consideration of inpatient therapy
		*The combination of heart failure and chronic lung disease defines cardiopulmonary disease

Other Scores

- Identifying Outpatients with DVT at low risk
 - Patient Population: All patients with acute DVT in the lower limbs
 - Assessed clinical outcome \leq 15 days at the start of treatment
 - Bilateral DVT, renal insufficiency, body weight <70 kg, recent immobility, chronic heart failure, and cancer were associated with an increased risk for adverse outcomes
 - Conclusion: A risk score with easily available variables can be created to identify if DVT patients should be available for ambulatory treatment (treatment without admission to the hospital)
- Cancer Patients at increased risk of death
 - Considered the 3-month mortality of patients with VTE and cancer
 - Mortality rate was 7.9% in the RIETE population
 - 26.4% of patients with cancer died while 4.1% of patients without cancer died
 - Conclusion: Cancer was the strongest factor for PE related mortality

Other Scores cont.

- Predictors for fatal PE
 - 15,520 patients with VTE
 - Conclusions:
 - Patients with symptomatic non massive PE at presentation had 5.42-fold higher risk of fatal PE than those without
 - Risk of fatal PE was multiplied by 17.5 in patients presenting with a symptomatic massive PE
- Identifying cancer patients with PE at low risk
 - Objective: Develop a risk score to determine 30 day mortality in patients with PE and cancer
 - Risk Factors: age > 80 years, heart rate \geq 110/min, systolic BP < 100 mm Hg, body weight < 60 kg, recent immobility, and presence of metastases

Registry	Population	Patient Population	Follow-Up	Duration	Centers
RIETE Registry	124,602	Patients with acute DVT or PE	≥ 3 months	2001-present	210
GARFIELD Registry	10,869	Patients with acute VTE within 30 days of diagnosis	≥ 3 years	2009-2019	~500
TROLL Registry	5,037	≥ 18 years with VTE that included DVT, PE, splanchnic vein thrombosis, or cerebral sinus vein thrombosis	≥ 3 weeks	2005-present	1
PREFER Registry	3,545	Acute VTE that manifested as distal or proximal DVT and/or PE	1 year	2013-2014	381

Acknowledgements

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References

1. [The venous thrombosis registry in Østfold Hospital \(TROLL registry\) - design and cohort description - PMC](#)
2. [Global Anticoagulant Registry in the Field – Venous Thromboembolism \(GARFIELD-VTE\)](#)
3. [One-year incidence of venous thromboembolism, bleeding, and death in patients with solid tumors newly initiating cancer treatment: Results from the Cancer-VTE Registry - ScienceDirect](#)
4. [The management of acute venous thromboembolism in clinical practice - study rationale and protocol of the European PREFER in VTE Registry](#)
5. [VTE Registry: What Can Be Learned from RIETE? - PMC](#)
6. <https://rieteregistry.com/>
7. [Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism](#)
8. [Three-month mortality rate and clinical predictors in patients with venous thromboembolism and cancer. Findings from the RIETE registry](#)
9. [Predicting adverse outcome in outpatients with acute deep vein thrombosis. findings from the RIETE Registry](#)
10. [Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa \(RIETE\) Registry](#)
11. [A clinical prognostic model for the identification of low-risk patients with acute symptomatic pulmonary embolism and active cancer](#)