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"Predictive Role of Prothrombotic Markers in Early Detection of Deep Vein Thrombosis among Metabolic Syndrome Patients"

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Introduction

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a significant but preventable vascular disease that causes the formation of blood clots in the venous system of the body. VTE is recognized globally as the third most common cardiovascular disease, following myocardial infarction and stroke, with significant morbidity and mortality [1]. Epidemiological studies have shown that approximately 1 in 1000 adults in the world is affected by venous thromboembolism (VTE) each year, with the prevalence of VTE increasing with age, hospitalization, and the presence of various medical illnesses [2]. Of all VTE cases, DVT accounts for approximately two-thirds of all VTE cases, whereas pulmonary embolism (PE) accounts for the remaining cases. One of the most significant long-term complications of DVT is the development of post-thrombotic syndrome (PTS). This condition occurs in 40-50% of patients within the first few years of the onset of the disease [3]. Further, in more serious cases, part of the thrombus may break off and travel in the bloodstream to lodge in the pulmonary vessels, thereby causing pulmonary embolism. PE is a life-threatening complication. It is responsible for causing considerable mortality among patients with VTE. Though significant advances have been made in the management of VTE with anticoagulant or thrombolytic therapy, VTE is still a significant clinical concern because of its tendency to cause recurrence. Studies have indicated that there is a 20–30% chance of recurrence of VTE in patients in ten years following the first episode, especially in patients with persistent risk factors or metabolic disorders [4]. Recently, metabolic syndrome (MetS) has emerged as an important factor that may be associated with the development or recurrence of venous thrombosis. Metabolic syndrome is defined as a group of metabolic disorders that include central obesity, hypertension, insulin resistance, hyperglycemia, and dyslipidemia with high triglycerides and low high-density lipoproteins (HDL) in the blood [5]. Over the past few decades, there has been a significant increase in the prevalence of metabolic syndrome in the global population. Metabolic syndrome affects almost 30–45% of adults in many countries due to an increase in obesity [6].

Increasing evidence suggests that metabolic syndrome can induce a pro-inflammatory, pro-thrombotic condition, which can predispose individuals to VTE. The co-existence of various components of metabolic syndrome can induce several pathophysiological changes, including endothelial dysfunction, platelet hyperreactivity, chronic low-grade inflammation, coagulation, and impaired fibrinolysis [7]. Adipose tissue, particularly visceral fat, is an active endocrine organ that produces pro-inflammatory cytokines, adipokines, such as leptin and adiponectin, which affect vascular homeostasis and coagulation pathways. Moreover, an increase in levels of plasminogen activator inhibitor-1 (PAI-1) in individuals with metabolic syndrome can inhibit fibrinolysis, thus predisposing them to thrombosis [8]. These mechanisms induce a hypercoagulable state, which can increase the incidence of VTE in patients with metabolic syndrome, including the recurrence of VTE. Various methods, including clinical probability scores, D-dimer, are used for the clinical diagnosis of VTE. These methods are commonly used in clinical practice for the diagnosis of VTE. These methods, however, have some limitations. For instance, an increase in levels of D-dimer can also be observed in other

clinical conditions, such as infections, inflammation, trauma, or in the postoperative period, which can lead to unnecessary imaging investigations [9]. Thus, there is an increasing interest in identifying new markers for the early diagnosis of VTE, which can predict recurrence in patients with VTE, including those with metabolic syndrome. Various markers, such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), adipokines, endothelial markers, coagulation markers, etc., have been studied in recent years [10]. These markers are of particular interest because most of them can be measured by routine blood counts, which can be used for clinical purposes.

Advances in molecular biology have also led to the introduction of emerging biomarkers, which include microRNAs and metabolomic profiles. This may lead to further insights into the molecular pathways that connect venous thrombosis and metabolic dysfunction [11]. This may also lead to the early identification of people who are at increased risk of developing thrombosis, although they are yet to show symptoms [12]. It is essential to understand the relationship between metabolic syndrome and VTE in order to improve diagnostic techniques and develop effective prevention techniques [13]. It is essential to understand that the risk of developing VTE is not the same among all populations. Gender, ethnicity, and geographical distribution are some of the factors that affect the risk of developing the disease [14]. For example, women are at increased risk of developing VTE due to hormonal influences, pregnancy, and the use of oral contraceptives [15]. Additionally, genetic predispositions and environmental factors may be the reason behind the risk of developing VTE among different ethnic groups [16].

As the incidence of metabolic syndrome continues to escalate worldwide and evidence of the role of this syndrome in venous thrombosis mounts, the need for a better understanding of the molecular mechanisms that connect these diseases becomes even more important [17]. In addition, the discovery of reliable biomarkers may help in the early diagnosis and management of the disease [18]. In this regard, this review aims to give a comprehensive overview of the pathophysiological mechanisms that connect metabolic syndrome and venous thromboembolism, especially in relation to circulating biomarkers [19]. In addition, this review will look into both traditional and new biomarkers of thrombosis, their significance, and how they may be used for the early diagnosis and management of DVT [20]

Search Strategy

To explore the association of metabolic syndrome with VTE, the literature search was carried out with emphasis on the biomarkers that are responsible for the early detection of the disease and the recurrence of VTE. The most important databases were searched with the keywords such as “deep vein thrombosis,” “venous thromboembolism,” “metabolic syndrome,” “obesity,” “adipokines,” “microRNA,” etc., and the Boolean operators such as AND and OR. The review is based on the peer-reviewed articles that were published in the range of 2000-2024. The emphasis was given to the recent studies. The studies were selected based on the relevance to the mechanisms of the disease and the role of metabolic syndrome in the development of VTE. The studies that were carried out on the basis of the gender and ethnic variations were also taken into consideration. The reference lists of the relevant studies were also searched. The above-mentioned methods were useful in providing a general overview of the recent studies on the topic of metabolic syndrome-related venous thrombosis and the role of serum biomarkers in the early detection of the disease.

Epidemiology, Prevalence, and Recurrence of VTE in Metabolic Syndrome

Venous thromboembolism (VTE), which includes DVT and PE, is considered to be a critical health problem that has significant implications for cardiovascular health and mortality worldwide **[1]**. VTE is recognized as the third most common cardiovascular disease, following myocardial infarction and stroke **[1]**. According to research findings, VTE affects about 1-2 people per 1000 every year, and the risk increases with age, hospitalization, cancer, surgery, and metabolic disorders **[2]**. Although the prevalence of VTE is low among the younger population, the risk increases dramatically among people aged above

60 years **[24]**. Apart from the health-related problems, VTE has the potential to cause subsequent complications, which include post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension **[25]**. Both of these conditions are likely to impair the physical functioning of the patient **[26]**. Although there is some improvement in the prevention and treatment of VTE, the risk of death is still high among people suffering from the disease **[27]**. PE is the leading cause of death among people suffering from VTE, and the disease is responsible for the death of hundreds of thousands of people worldwide each year **[28]**. Apart from the health-related problems, VTE is likely to cause significant economic burden due to hospitalization, the use of anticoagulants, and the risk of subsequent thrombosis **[29]**.

Prevalence and Burden of Metabolic Syndrome in VTE

Metabolic syndrome (MetS) refers to a group of metabolic abnormalities that include central obesity, hypertension, insulin resistance, hyperglycemia, elevated triglycerides, and low levels of high- density lipoprotein (HDL) cholesterol **[5]**. Over the past several decades, the prevalence of metabolic syndrome has increased significantly across the world, largely due to lifestyle changes, poor dietary habits, and reduced physical activity. Current estimates suggest that around 30–45% of adults in many populations are affected by metabolic syndrome, making it a major global public health issue **[6]**. Research increasingly shows that metabolic syndrome is strongly associated with a higher risk of venous thromboembolism **[30]**. Metabolic syndrome (MetS) is associated with several metabolic changes that can promote the development of blood clots. These disturbances contribute to chronic low-grade inflammation, dysfunction of the vascular endothelium, increased platelet activation, and reduced fibrinolysis, all of which create a pro-thrombotic environment **[7]**. Among the components of metabolic syndrome, abdominal obesity and insulin resistance are considered particularly important in the development of thrombosis **[31]**. Visceral fat is not just a passive fat store; it functions as an active endocrine tissue that releases inflammatory cytokines and adipokines, which can disrupt normal vascular function **[32]**. As a result, the production of procoagulant factors such as fibrinogen and plasminogen activator inhibitor-1 (PAI-1) may increase. Elevated levels of these factors reduce fibrinolysis and promote the formation of blood clots **[8]**.

Recurrence Risk in Obesity and Metabolic Syndrome

One of the major problems in dealing with venous thromboembolism (VTE) is that it is prone to recurrence **[4]**. Long-term studies indicate that 20-30% of patients may be at increased risk for recurrence within ten years of experiencing their first VTE event, especially if underlying risk factors persist in their system **[33]**. In recent times, obesity and metabolic syndrome have also been identified as playing a significant role in elevating the risk for recurrence **[34]**. For example, in a recent study by Stewart and Kline (2020), it was found that people suffering from metabolic syndrome were significantly at increased risk for recurrence after experiencing their first VTE event **[35]**. Moreover, people who had co-occurring metabolic syndrome had a higher risk for recurrence compared to those without metabolic disorders **[36]**. This indicates that metabolic syndrome may be acting as a persistent prothrombotic state rather than an acute risk factor for VTE recurrence.

Previous studies have also pointed to the fact that obesity is an essential factor in the occurrence of VTE relapse **[37]**. The studies done by Ageno and other epidemiological studies have pointed to the fact that people who have a higher BMI are more likely to be at risk of experiencing first-time and recurrent events of VTE **[38]**. This is mainly because of the prothrombotic state that is brought about by the inflammation, coagulation factors, and reduced fibrinolysis that is associated with obesity **[39]**

Mortality and Clinical Severity

The presentation of venous thromboembolism differs significantly in different people. While some people may be asymptomatic for the disease, others may be at risk of experiencing life-threatening conditions such as pulmonary embolism [28]. In addition to the immediate threat of death resulting from the disease, the recurrence of the disease may also result in future health complications that may be costly

to the healthcare system in the long term [29]. The outcome of the disease in people suffering from metabolic syndrome may be severe because they are likely to suffer from coexisting conditions such as type 2 diabetes, hypertension, and cardiovascular disease [5]. This may make the management of the disease complicated and may also result in the side effects experienced by the patient when they take the drugs to manage the disease [27].

Importance of Metabolic Syndrome in VTE Epidemiology

The association of metabolic syndrome and venous thromboembolism is of significant importance in the present scenario, as the incidence of metabolic syndrome is rising worldwide [6]. As the prevalence of obesity and insulin resistance is rising, people in the future might be more likely to suffer from blood clotting disorders [31]. The awareness of the importance of metabolic syndrome as a risk factor for venous thromboembolism can help healthcare professionals to identify people who are more likely to develop VTE in the future and take steps to prevent it [30]. However, as metabolic syndrome is considered to be a long-term risk factor for venous thromboembolism, monitoring and prevention are of utmost importance to reduce the chances of recurrent venous thromboembolism in patients with metabolic syndrome [4]. Simple measures such as maintaining physical weight, having a healthy and balanced diet, and managing metabolic syndrome can be of significant importance in reducing the risk of venous thromboembolism in patients with metabolic syndrome **[40]**.

Pathophysiology of Venous Thrombosis in Metabolic Syndrome

Venous thromboembolism (VTE) is a multifactorial disease that is defined as the formation of thrombi in the venous system, especially in the deep veins of the lower limbs **[1]**. This is an important clinical condition that has the potential to cause morbidity and mortality **[3]**. The formation of venous thrombosis is influenced by various factors, including hemodynamic changes, vascular structural changes, and changes in the composition and properties of blood **[7]**. Metabolic syndrome is defined as a cluster of metabolic disorders that include central obesity, insulin resistance, dyslipidemia, and hypertension **[5]**. This condition is increasingly being recognized as an important risk factor for venous thrombosis **[30]**. The metabolic syndrome is associated with a number of biochemical and cellular changes that result in a prothrombotic state **[7]**. This means that people with metabolic syndrome are at an increased risk of developing venous thrombosis due to changes in the coagulation system, vascular integrity, and hemodynamics **[7]**.

At the molecular level, metabolic syndrome is associated with an increase in proinflammatory cytokines, adipokines, and reactive oxygen species **[7]**. These factors are responsible for endothelial dysfunction, which is an essential step in the development of thrombotic processes **[7]**. Endothelial dysfunction leads to alterations in the functional role of the endothelium, which maintains an antithrombotic and vasodilatory role. Endothelial dysfunction leads to vasoconstriction, platelet adhesion, and activation of coagulation pathways **[7]**. Moreover, insulin resistance and hyperglycemia contribute to endothelial dysfunction **[5]**.

The second key factor in the development of metabolic syndrome is the imbalance in the coagulation process, which leads to a hypercoagulable state **[7]**. This is confirmed by an increase in coagulation factors such as fibrinogen, factor VII, and factor VIII, as well as an increase in the activity of plasminogen activator inhibitor-1, which inhibits the process of fibrinolysis **[8]**. Moreover, platelet hyperactivity is also observed in metabolic syndrome **[7]**.

The imbalance in the coagulation process leads to a shift towards the formation of thrombi rather than their dissolution **[7]**. Hemodynamic factors also have an important role to play in the pathogenesis of venous thrombosis in metabolic syndrome **[7]**. Obesity and physical inactivity, which are commonly associated with metabolic syndrome, contribute to venous stasis by affecting venous return and the efficiency of the skeletal muscle pump **[31]**. An increase in intra-abdominal pressure, which is associated

with central obesity, also compromises venous return, particularly in the lower limbs **[31]**. This compromises venous return, leading to venous stagnation, which facilitates the interaction of coagulation factors with the endothelium, thus leading to thrombus formation **[7]**. Adipose tissue, particularly visceral adipose tissue, is an active endocrine organ that produces various bioactive substances, which include leptin, resistin, and pro-inflammatory cytokines **[32]**. These factors have all been shown to contribute to thrombogenesis **[7]**. The cumulative effects of all these factors, therefore, lead to a pro-inflammatory and pro-thrombotic state, which significantly increases the risk of venous thromboembolism in patients with metabolic syndrome **[7]**.

It is, therefore, evident that the pathophysiology of venous thrombosis in metabolic syndrome is not due to a single factor, but rather the cumulative effects of various factors, which include metabolic, pro-inflammatory, and pro-thrombotic factors, leading to an imbalance in the delicate balance of pro-thrombotic and anti-thrombotic factors, thus leading to thrombus formation **[7]**.

This complex process can be better understood through established conceptual frameworks and anatomical considerations, which are discussed in the following sections

Virchow's Triad

However, the concept of Virchow's triad is still of great value in understanding venous thrombosis **[7]**. The first factor in Virchow's triad is venous stasis. This is defined as the slowing or stopping of the blood in the veins **[7]**. The slowing of the blood in the veins does not directly cause venous thrombosis. However, it does play a part in it. The slowing of the blood in the veins allows the coagulation factors to accumulate in the blood. This, in turn, leads to venous thrombosis **[7]**. The slowing down of the blood in the veins also means that it is not diluted with coagulating factors, which in turn leads to venous thrombosis. The second factor in Virchow's triad is damage to the endothelium. This is damage to the inner surface of the veins **[7]**. This damage to the inner surface of the veins leads to inactivation of the anti-coagulant properties of the veins. When the inner surface of the veins is damaged, it leads to exposure of the underlying collagen. This, in turn, leads to venous thrombosis **[7]**. There are many clinical situations that lead to damage to the inner surface of the veins. This damage in turn leads to venous thrombosis. This includes surgery, trauma, immobilization, heart failure, and cancer **[23]**. The third factor in Virchow's triad is hypercoagulability. This is the imbalance of the procoagulant and anticoagulant factors in the blood **[7]**. This could be inherited or acquired. Hypercoagulability could be caused by inherited disorders such as factor V Leiden mutation, obesity, cancer, hormone replacement therapy, and inflammatory disease **[31]**. This increases the risk of venous thrombosis through the increase of coagulation factors, which in turn increases the levels of thrombin **[7]**.

Sites and Mechanisms of Venous Thrombus Formation

The most common sites for venous thromboembolism are those with slow or interrupted blood flow **[7]**. In the deep veins in the legs, the most common sites are the pockets in the valves **[7]**. In the veins, the presence of the valves helps the blood move upwards towards the heart. However, the area after the valves sometimes has slow blood flow. In the event that there is stagnation of blood in this area, the oxygen saturation is reduced, and this leads to hypoxia **[7]**. The presence of hypoxia in the blood activates the endothelial cells **[7]**. In the presence of low oxygen in the blood, the endothelial cells overexpress the adhesion molecules such as P-selectin **[7]**. The presence of these adhesion molecules attracts the platelets and white blood cells. The white blood cells with tissue factors bind to the endothelial cells and initiate the clotting process **[7]**. The role of tissue factor in the formation of thrombi is significant. It is involved in the activation of thrombin formation, activation of coagulation, and deposition of fibrin **[27]**. The venous thrombus is composed of various structures, which include an outer layer of fibrin with red blood cells, an inner layer of platelets, strands of extracellular DNA, which are derived from neutrophils that are activated to form neutrophil extracellular traps, which in turn leads to the stabilization of the

thrombus, enlargement of the thrombus, interaction with platelets, thus improving the thrombotic process **[40]**.

Under normal conditions, various physiological mechanisms of anticoagulation are in place that help in controlling blood clots and maintaining the balance in the process of hemostasis **[41]**. The physiological mechanisms of anticoagulation include the protein C and S complex, the antithrombin complex, and tissue factor inhibitors **[42]**. However, when the balance is disturbed in the process of hemostasis, the risk of thrombosis is increased **[29]**.

Mechanisms by Which Metabolic Syndrome Increases Thrombotic Risk

Metabolic syndrome also causes venous thrombosis through different but related mechanisms. Among all the different Similarly, metabolic syndrome also leads to venous thrombosis through different, though related, pathways **[7]**. Out of all the different manifestations of metabolic syndrome, obesity and insulin resistance have been found to play a major role in venous thrombosis **[31]**. In people suffering from metabolic syndrome, adipose tissue acts as an active endocrine organ **[32]**. This adipose tissue releases various different inflammatory mediators or adipokines. High levels of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) activate endothelial cells and stimulate coagulation **[7]**. On the other hand, low levels of anti-inflammatory adipokines like adiponectin impair endothelial function and activate platelets **[32]**.

Moreover, the pro-inflammatory state of obesity is also related to elevated levels of plasminogen activator inhibitor-1 (PAI-1), which is involved in the inhibition of fibrinolysis and affects the process of fibrin clot degradation **[8]**. This could potentially cause an increase in the longevity of thrombi in the circulation, which in turn could cause an increased incidence of VTE recurrence **[4]**. Another factor that could be of crucial importance in the hypercoagulable state of patients with metabolic syndrome is insulin resistance, which could potentially cause hypercoagulability in patients with metabolic syndrome through the promotion of oxidative stress, endothelial dysfunction, and increased platelet reactivity **[5]**. The metabolic changes could potentially cause hypercoagulability in patients with metabolic syndrome and make them more prone to venous thrombosis **[7]**. Moreover, patients with metabolic syndrome have elevated levels of different coagulation factors in their circulation, such as fibrinogen, factor VII, and factor VIII, and also elevated platelet activity, which could potentially cause hypercoagulability and the formation of thrombi in the venous system **[7]**.

Platelet–Neutrophil–Lymphocyte Crosstalk and Thrombo-Inflammation

Recently, the interaction of platelets, neutrophils, and lymphocytes in venous thrombosis has gained significant importance **[40]**. The activation of neutrophils in thromboinflammation is significant, as neutrophils are responsible for the formation of neutrophil extracellular traps, which are structures that promote thromboinflammation by increasing the formation of fibrin and platelet activation **[40]**. Moreover, platelet activation can interact with neutrophils through adhesion molecules, thus increasing thromboinflammation **[7]**. Simultaneously, decreased levels of lymphocytes have also been observed in states of inflammation due to systemic immune activation **[7]**.

The interaction of platelets, neutrophils, and lymphocytes in venous thrombosis has thus provided new markers of inflammation, such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) **[10]**. An increase in the levels of NLR and PLR thus indicates increased neutrophil activation, platelet activation, and decreased levels of lymphocytes, thus indicating a high level of thromboinflammation **[10]**. Thus, new markers of inflammation have been studied for their potential to predict thromboinflammation in patients with VTE.

The interaction of platelets, neutrophils, and lymphocytes in venous thrombosis thus provides valuable insights into the association of metabolic syndrome with venous thrombosis **[7]**. Moreover, this interaction also provides valuable insights into the increasing interest in the use of markers for the early diagnosis of VTE **[10]**.

Biomarkers for Early Identification of DVT in Patients with Metabolic Syndrome

Biomarkers linked to deep vein thrombosis (DVT) in individuals with metabolic syndrome (MetS) can generally be grouped into several categories, including inflammatory markers, platelet-related markers, adipokine markers, lipid-related markers, endothelial and coagulation markers, as well as newer omics-based biomarkers **[10]**. This classification is helpful because metabolic syndrome contributes to thrombosis through multiple overlapping biological processes, such as chronic inflammation, dysfunction of adipose tissue, endothelial damage, platelet activation, and reduced fibrinolysis **[7]**.

At present, no single biomarker is able to independently diagnose DVT associated with metabolic syndrome **[41]**. However, using traditional laboratory markers together with newly identified biomarkers may enhance early detection, help evaluate the risk of recurrence, and provide a better understanding of the underlying mechanisms involved in the disease **[42]**.

Conventional and Clinically Relevant Biomarkers

Among all the tests currently available, D-dimer as a marker of DVT diagnosis has been the most frequently used **[9]**. This is because it plays a significant role in the formation and degradation of fibrin **[9]**. However, it has also been observed that D-dimer lacks sufficient specificity, as it can be raised in patients suffering from diseases like infection, inflammation, cancer, trauma, pregnancy, and old age **[9]**. Therefore, in patients suffering from metabolic syndrome, where the level of inflammation may already be raised, D-dimer as a diagnostic test should always be used as part of a structured algorithm **[21]**. Other important biomarkers that can be used for the diagnosis of patients suffering from metabolic syndrome include CRP, mean platelet volume, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and lipid-related biomarkers like HDL and Apo A1 **[10]**. These tests can be carried out as part of routine blood tests, and since they are non-invasive, they are cost-effective. Although these tests may not help in the diagnosis of patients suffering from metabolic syndrome, they can still give useful information **[10]**

Adipokine Biomarkers

Adipokines are particularly important when studying thrombosis in metabolic syndrome because they directly connect visceral obesity, chronic inflammation, endothelial dysfunction, and coagulation abnormalities. In obesity and MetS, adipose tissue undergoes structural and metabolic changes, including cell enlargement, local hypoxia, macrophage infiltration, and inflammatory remodeling. These changes increase the production of proinflammatory mediators such as leptin, interleukin-6, tumor necrosis factor-α, and plasminogen activator inhibitor-1 (PAI-1), while reducing levels of protective adipokines such as adiponectin **[32,8]**. The combined effect of these alterations promotes endothelial activation, reduced fibrinolysis, enhanced platelet activity, and increased coagulation factor expression, thereby creating a prothrombotic environment **[7]**.

Adiponectin

Adiponectin possesses anti-inflammatory, endothelial-protective, and possibly antithrombotic effects **[43]**. It is also known that levels of adiponectin are generally lower in people with obesity, insulin resistance, and central adiposity **[32]**. It was proposed that higher levels of adiponectin could offer protection from VTE, whereas lower levels could increase the risk of VTE in patients with metabolic syndrome **[44]**. For instance, in a study by Mrozinska et al., it was demonstrated that lower levels of adiponectin, which were determined after DVT, were associated with an increased risk of PTS, regardless of the presence of obesity **[45]**. This again emphasizes the importance of adipokine imbalance in the context of VTE.

Leptin

Leptin is known to be a pro-inflammatory adipokine, and its concentration is known to rise with increasing adiposity **[32]**. Leptin is also known to be involved in endothelial cell activation, platelet activation, and procoagulant pathways **[7]**. A Mendelian randomization analysis carried out in 2023 found that higher

circulating leptin is associated with an increased risk of VTE, DVT, and pulmonary embolism, whereas adiponectin is found to have protective effects **[46]**. Therefore, it is proposed that this balance of leptin and adiponectin plays an important role in thrombotic complications in metabolic syndrome **[7]**.

Inflammatory Biomarkers

Inflammation is an essential aspect of venous thrombosis, especially in patients with metabolic syndrome **[7]**. One of the most commonly investigated markers of inflammation in the context of VTE is C-reactive protein (CRP). The results of the cohort study based on the ARIC data revealed that elevated CRP is independently associated with the incidence of VTE **[47]**. However, it is not considered a specific marker of DVT and should be regarded as an inflammatory marker rather than a VTE biomarker **[10]**. High-sensitivity CRP (Hs-CRP) could be more informative in the context of VTE in the prognostic setting **[48]**. The results of the studies of cancer-associated thrombosis indicate that VTE recurrence could be predicted based on the results of measurements of Hs-CRP after discontinuation of anticoagulant therapy and D-dimer in cancer patients **[49]**. Elevated Hs-CRP in patients with metabolic syndrome could be associated with not only ongoing metabolic inflammation but also thrombotic risk **[7]**.

Lipid-Associated Biomarkers

Alterations in lipid metabolism are major components of metabolic syndrome, with several studies examining the link between HDL, ApoA1, and ratios of lipoproteins with VTE **[50]**. Previous work indicated that elevated levels of HDL and ApoA1 may be associated with reduced risk of recurrent VTE **[51]**. However, more recent studies have provided inconsistent results. Some have indicated that patients with DVT or PE have reduced levels of HDL, while others have not found any strong association with first-time VTE events **[52]**.

In relation to metabolic syndrome, lipid levels should be regarded as background markers of metabolic and vascular risk rather than being used in any way in the diagnosis of VTE **[5]**. A reduced level of HDL, increased triglycerides, and abnormal ApoB/ApoA1 ratios may all be associated with endothelial dysfunction and underlying vascular inflammation **[7]**. However, in relation to DVT, they have little value in diagnosis **[10]**.

Platelet-Related Biomarkers Mean Platelet Volume (MPV)

MPV is an accessible platelet index that indicates the platelet volume and activity **[10]**. The Tromso study showed that elevated levels of MPV were linked with the risk of developing VTE and unprovoked VTE **[53]**. The study supported the role of platelet activation in VTE **[7]**. However, studies have reported conflicting data on the MPV levels and VTE **[54]**. Therefore, it is important to approach the MPV levels with caution **[10]**.

Thromboxane A2

Thromboxane A2 is a platelet-derived mediator that stimulates vasoconstriction and platelet aggregation **[55]**. Although it is not measured in clinical practice, experimental studies indicate that it plays an important role in the development of venous thrombosis **[56]**. In one study by Tarantino et al., platelet-derived thromboxane was found to be involved in the development of venous thrombosis in animal models **[57]**. This indicates that platelet activation is involved in venous and arterial thrombosis **[7]**. In the context of the metabolic syndrome, in which platelet hyperreactivity is common, the role of the thromboxane pathways in the relationship between obesity and the risk of DVT is noteworthy **[31]**.

CBC-Derived Inflammatory Ratios

Complete Blood Count-derived ratios have shown promise as a useful, simple, and inexpensive tool for clinical practice **[10]**. Among these ratios, the Neutrophil-to-lymphocyte ratio and the Platelet-to-lymphocyte ratio are of particular significance, as they are indicative of thromboinflammatory processes in MetS-related DVT **[10]**.

Neutrophil-to-Lymphocyte Ratio (NLR)

NLR is an indicator of the interplay between neutrophil-mediated inflammation and lymphocyte suppression **[10]**. Neutrophils also cause thrombosis by forming neutrophil extracellular traps (NETs) and activating tissue factor-mediated coagulation **[40]**. A 2022 study's meta-analysis indicated that NLR had moderate value in diagnosing VTE **[58]**. A 2023 study's meta-analysis on DVT also indicated that NLR had sensitivity and specificity in diagnosing DVT, thus making it an adjunctive tool in diagnosing DVT **[59]**.

Platelet-to-Lymphocyte Ratio (PLR)

PLR is related to the level of platelet activation and the level of inflammation in the body **[10]**. As metabolic syndrome is associated with hyperreactive platelets and inflammation, the PLR is clinically pertinent in this case **[7]**. According to the meta-analysis of 2023, the PLR also has moderate diagnostic potential in DVT, although the heterogeneity of the data is still large **[60]**.

Combined Interpretation of NLR and PLR

The value of NLR and PLR may be maximally utilized if used in conjunction with each other, especially in conditions of obesity, metabolic syndrome, malignancy, or postoperative inflammatory conditions **[10]**. Literature has demonstrated that patients with conditions of acute DVT have higher levels of white blood cell count, neutrophil count, platelet count, NLR, PLR, and MPV in comparison with healthy controls **[61]**.

Clinical Use Protocol

NLR and PLR should be used as adjuncts rather than alternatives to other diagnostic tests like D-dimer and compression ultrasonography **[21]**. The appropriate place for NLR and PLR is in the diagnosis of:

- Suspected DVT in patients with significant inflammatory/metabolic burden **[10]**
- Thrombosis in obese and metabolic syndrome patients **[31]**
- Cancer-associated thrombosis **[49]**
- Evaluation for recurrence in acute VTE **[4]**

However, in patients with sepsis, infections, hematologic disorders, steroid therapy, and major inflammatory disorders, NLR and PLR need to be used cautiously due to significant effects on leukocyte and platelet counts **[61]**.

Endothelial and Coagulation Biomarkers

Tissue Factor and Tissue Factor–Bearing Microparticles

Tissue factor (TF), the main initiator of the extrinsic coagulation cascade, is believed to be involved in thrombosis in the context of inflammation **[56]**. It has been found that elevated tissue factor activity is present in cancer thrombosis, although its predictive value is variable depending on cancer types and methods of evaluation **[62]**. Moreover, elevated TF-bearing microparticles in cancer patients with VTE have also been reported, indicating their potential role as markers of the procoagulant status of the circulation in cancer patients **[63,64]**.

Von Willebrand Factor and Factor VIII

Endothelial activation markers, including von Willebrand factor (VWF) and factor VIII, have also been linked with an increased risk of VTE **[65]**. High levels of VWF have been associated with both incident VTEs and long-term venous complications **[66]**. Experimental studies have suggested that thromboinflammatory mechanisms involving VWF may be involved in obesity-associated thrombosis **[67]**. Although these markers have been strongly linked with VTE risk, they have not been used for routine clinical diagnosis **[10]**.

Emerging Biomarkers MicroRNA

MicroRNAs are small non-coding RNAs that play a role in regulating gene expression involved in endothelial cell function, inflammation, platelet activation, and blood coagulation **[68]**. Based on these roles, microRNAs have been studied as a potential biomarker for venous thrombosis **[69]**. Nevertheless, the clinical applicability of microRNAs as a biomarker for venous thrombosis is still not fully realized **[70]**. A study on the diagnostic potential of microRNAs as a biomarker for DVT found that miR-145-5p had a relatively low accuracy for the diagnosis of acute DVT, and further studies are required before it can be applied in clinical settings **[71]**.

Metabolomics

Metabolomics has been recognized as a potential tool in the discovery of new biomarkers, as it is more focused on the analysis of the metabolic changes occurring in the body during the process of disease **[72]**. Studies have recently identified the metabolomic patterns in the body of patients suffering from acute VTE, which could be potential diagnostic markers in the future **[73]**. However, more research is required in this direction before the metabolomic markers could be implemented in the real world **[74]**.

Comparative Evaluation of Biomarkers in MetS-Associated DVT

The growing number of biomarkers being studied in relation to VTE is an indication of the complex biological mechanisms that occur in thrombosis, especially in patients with metabolic syndrome **[7]**. The differences in the studied biomarkers include their biological source, diagnostic accuracy, availability, cost, and validation **[42]**. Some of the studied biomarkers have already been implemented in clinical practice, but others have not **[42]**. However, they may be valuable in the future in relation to early detection, recurrence prediction, and personalized risk assessment of thrombosis **[42]**. A comparative analysis of all the studied biomarkers is significant in establishing which ones are more valuable in clinical practice in relation to DVT in patients with metabolic syndrome **[42]**. Generally, studied biomarkers have been classified according to their utility in clinical practice into diagnostic, recurrence, metabolic syndrome-related, and research biomarkers **[42]**. Another difference in studied biomarkers is that some routine low-cost biomarkers have been developed from routine laboratory tests, while others have been developed using other techniques **[42]**

Diagnostic Biomarkers

Diagnostic biomarkers are mainly used for the detection and exclusion of DVT in patients who present with symptoms suggestive of venous thrombosis **[21]**. Among the available biomarkers, D-dimer is the most commonly used diagnostic biomarker for DVT **[9]**. An increase in D-dimer levels is associated with fibrin degradation products. This indicates that coagulation and fibrinolysis are occurring simultaneously **[9]**. When used in conjunction with clinical probability assessment tools like the Wells score, it is highly effective in ruling out DVT **[21]**. However, it is not very specific, as increased levels are also associated with other clinical disorders like infections, inflammation, cancer, trauma, and pregnancy **[9]**. Other biomarkers like C-reactive protein (CRP) and high-sensitivity CRP (Hs-CRP) have also been evaluated for their association with venous thrombosis **[47]**. Although it has been found that levels of CRP are increased in patients with DVT, it is not specific and is associated with other inflammatory disorders **[10]**. These biomarkers are therefore not recommended as specific biomarkers for the diagnosis of DVT. More recently, inflammatory biomarkers derived from routine complete blood count (CBC) parameters like the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have also been evaluated **[10]**. These are cheap, readily available, and may be indicative of the thrombo-inflammatory processes that occur in the formation of venous thrombi. Evidence from meta-analyses suggests that both NLR and PLR are of moderate value and may be useful adjuncts to well-established diagnostic tools such as D-dimer and ultrasound imaging **[58,60]**.

Prognostic and Recurrence Biomarkers

Apart from diagnosis, there are a number of biomarkers that have shown promise in the prediction of clinical outcomes and the risk of recurrent VTE **[42]**. Among them, Hs-CRP and D-dimer have shown promise in predicting VTE recurrence after discontinuation of anticoagulant therapy, especially in cancer-associated VTE **[49]**. Platelet-related biomarkers, such as mean platelet volume (MPV), have also shown promise **[53]**. The mean platelet volume is a measure of the size of platelets, and higher levels of MPV are indicative of a higher level of reactivity. Studies have shown that there may be a positive correlation between the levels of mean platelet volume and the risk of unprovoked VTE **[53]**. Lipid-related biomarkers, such as high-density lipoprotein (HDL) and apolipoprotein A1 (ApoA1), may also play a role in influencing the risk of VTE **[50]**. It has been shown that lower levels of HDL are associated with a higher risk of recurrent VTE, although this may not be true for all populations **[52]**.

Biomarkers Specifically Linked to Metabolic Syndrome

Amongst them, certain biomarkers have been of particular interest in relation to metabolic syndrome, as they have been associated with the underlying metabolic and pro-inflammatory processes that predispose individuals to thrombosis **[7]**. Of particular interest in relation to metabolic syndrome have been adipokines, which include adiponectin and leptin **[43]**. These have been implicated in linking obesity, insulin resistance, and inflammation with thrombosis **[7]**. Specifically, in individuals with metabolic syndrome, high levels of leptin and low levels of adiponectin have been associated with thrombosis due to their impact on endothelial dysfunction, platelet activation, and fibrinolysis **[7]**. Other thrombosis-associated biomarkers that have been linked with thrombosis in relation to metabolic syndrome include tissue factor, VWF, and factor VIII **[56,65]**. These have been associated with thrombosis in metabolic and inflammatory conditions. Specifically, high levels of VWF have been associated with both arterial and venous thrombosis **[65]**. Furthermore, high levels of VWF have been linked with endothelial damage in obesity-associated vascular disease **[67]**. Such thrombosis-associated biomarkers have provided valuable insights into the biological mechanisms that link metabolic syndrome with venous thrombosis **[7]**. Such biomarkers may also be used in the future to identify individuals at high risk of thrombosis **[42]**.

Biomarkers in Clinical Use vs. Research-Stage Biomarkers

From a practical point of view, it is also helpful to distinguish between routine clinical practice and research-based investigations **[42]**. Routine clinical practice-based biomarkers include D-dimer, C-reactive protein (CRP), mean platelet volume (MPV), and ratios of complete blood count results, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) **[10]**. However, an important drawback is that they have low specificity. Therefore, their results always have to be interpreted in conjunction with clinical findings and imaging results **[21]**. Furthermore, there are several other biomarkers that are still in the investigational phase **[42]**. These include microRNAs, metabolomics, and extracellular vesicle-associated tissue factor **[68,72,62]**. Some microRNA patterns have been suggested to be capable of identifying individuals at high risk of developing VTE **[69]**. Moreover, they may also be beneficial in gaining more insight into disease mechanisms. Some unique patterns have been recognized in patients with acute VTE **[70]**. Therefore, they may be beneficial in early diagnosis and risk stratification. However, they still have to be further validated for routine clinical practice **[74]**.

Diagnostic Value of Biomarkers: Sensitivity, Specificity, and Clinical Utility

From a practical point of view, it is also helpful to distinguish between routine clinical practice and research-based investigations **[42]**. Routine clinical practice-based biomarkers include D-dimer, C-reactive protein (CRP), mean platelet volume (MPV), and ratios of complete blood count results, including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) **[10]**. However,

an important drawback is that they have low specificity. Therefore, their results always have to be interpreted in conjunction with clinical findings and imaging results **[21]**. Furthermore, there are several other biomarkers that are still in the investigational phase **[42]**. These include microRNAs, metabolomics, and extracellular vesicle-associated tissue factor **[68,72,62]**. Some microRNA patterns have been suggested to be capable of identifying individuals at high risk of developing VTE **[69]**. Moreover, they may also be beneficial in gaining more insight into disease mechanisms. Some unique patterns have been recognized in patients with acute VTE **[70]**. Therefore, they may be beneficial in early diagnosis and risk stratification. However, they still have to be further validated for routine clinical practice **[74]**.

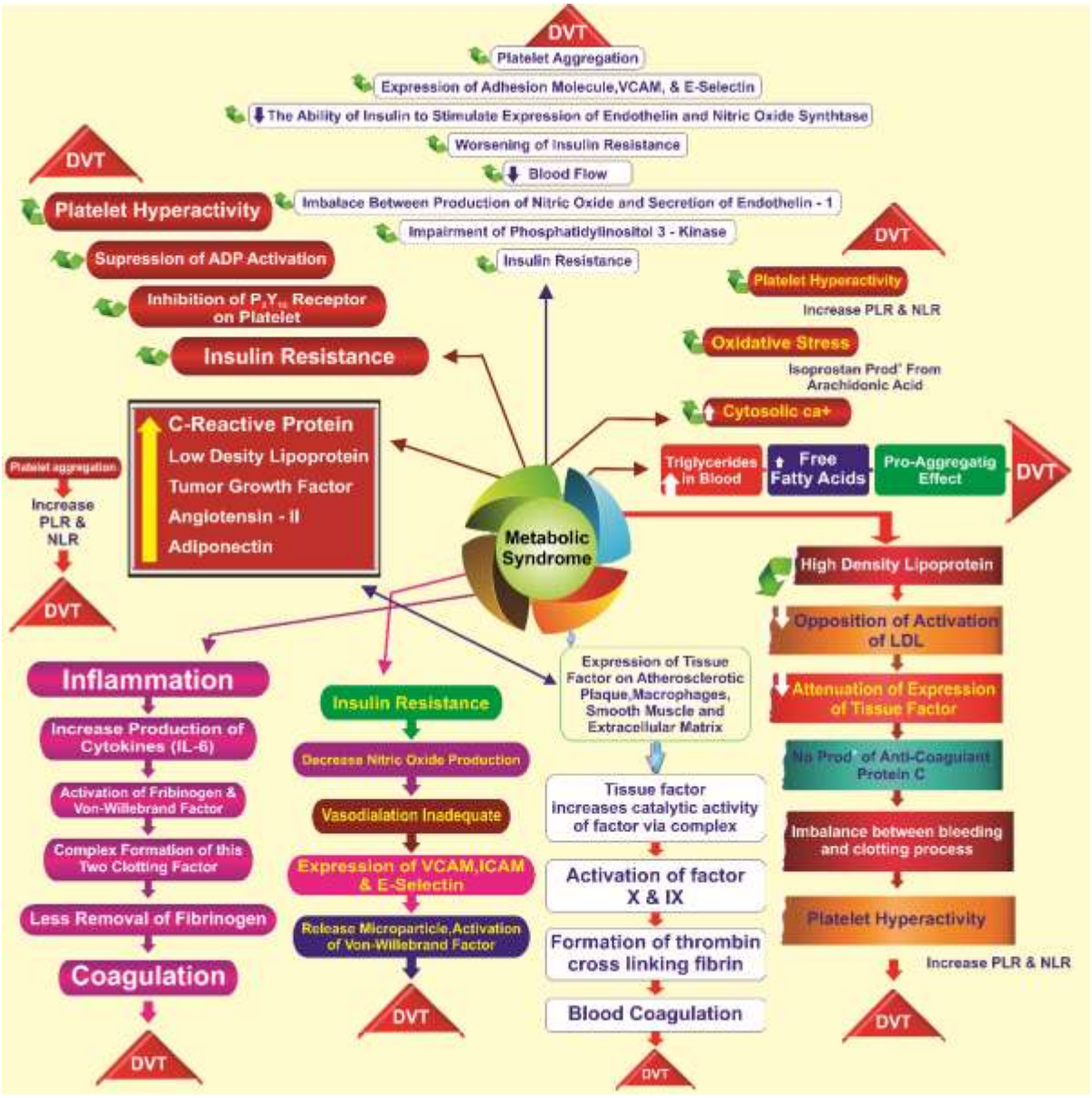
Other commonly studied markers, such as C-reactive protein, mean platelet volume, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio, are generally thought to be of secondary importance in the process of thrombosis, rather than playing a key role in the process **[10]**. These markers are thought to primarily reflect the process of inflammation associated with thrombosis, rather than directly reflecting the presence of thrombi **[10]**. These markers, however, may offer some useful ancillary information on the degree of inflammation associated with thrombotic risk in patients with metabolic syndrome **[7]**.

On the other hand, there are several other markers, including adipokines, endothelial injury markers, as well as emerging omics-based markers such as microRNAs and metabolomics, which are in the early stages of investigation **[43,65,68,72]**. These markers, although showing promise in the investigation of thrombosis, have not yet been adequately validated or standardized for clinical use **[74]**.

Diagnostic Algorithm for Suspected DVT in Patients with Metabolic Syndrome

For early detection of deep vein thrombosis (DVT) in patients with metabolic syndrome, there is a need for a systematic approach in diagnosing DVT **[21]**. This is usually carried out using a stepwise approach that combines clinical evaluation, risk assessment tools, laboratory-based investigations, and imaging techniques for accurate diagnosis of DVT in patients with metabolic syndrome **[21]**. Patients with metabolic syndrome have underlying conditions that include low-grade inflammation, endothelial dysfunction, platelet activity, and reduced fibrinolysis **[7]**. These underlying conditions increase the risk of thrombosis in patients with metabolic syndrome. Therefore, there is a need for a systematic approach in diagnosing DVT in patients with metabolic syndrome. A systematic approach in diagnosing DVT in patients with metabolic syndrome could be carried out using clinical scoring systems in conjunction with laboratory-based investigations **[21]**. The existing clinical guidelines suggest a stepwise approach in diagnosing the disease, which starts with symptom assessment and risk factor assessment, followed by laboratory investigations and imaging, if necessary **[21]**. In cases of metabolic syndrome, other laboratory tests such as the neutrophil-lymphocyte ratio and platelet-lymphocyte ratio can also be considered useful in providing supplementary information in relation to the underlying thrombo-inflammatory state of the patient **[10]**.

Fig No: 01 -"Mechanistic Pathways of Thrombogenesis in Metabolic Syndrome"



Biomarker	Biological Role	Diagnostic Use	Sensitivity	Specificity	Main Limitation	Clinical Status
D-dimer	Fibrin degradation product indicating active coagulation and fibrinolysis	Rule-out test for suspected DVT	High (~85–98%) [9]	Low–moderate [9]	Elevated in many conditions (infection, cancer, trauma, pregnancy) [9]	Routine clinical use
CRP / Hs-CRP	Systemic inflammatory marker reflecting inflammatory burden	Adjunctive marker for thrombosis risk and recurrence	Moderate [47]	Low [47]	Non-specific inflammatory marker [47]	Adjunct biomarker
Mean Platelet Volume (MPV)	Indicator of platelet size and activation	Possible marker of platelet-mediated thrombosis	Variable [42]	Variable [42]	Conflicting results across studies [42]	Investigational adjunct
Neutrophil-to-Lymphocyte Ratio (NLR)	Reflects neutrophil-driven inflammation and lymphocyte suppression	Inflammatory risk marker in suspected DVT	Moderate [10]	Moderate [10]	Influenced by infection and inflammatory diseases [10]	Adjunct biomarker
Platelet-to-Lymphocyte Ratio (PLR)	Reflects platelet activation and systemic inflammation	Risk stratification marker in thromboinflammatory conditions	Moderate [10]	Moderate [10]	Not specific for thrombosis [10]	Adjunct biomarker
Adiponectin	Anti-inflammatory adipokine regulating endothelial function	Potential MetS-related thrombosis biomarker	Not standardized [42]	Not standardized [42]	Limited clinical data and assay variability [42]	Research stage
von Willebrand Factor (VWF)	Endothelial activation and platelet adhesion	Marker of endothelial dysfuncti	Moderate [42]	Moderate [42]	Not specific for DVT [42]	Emerging biomarker

	mediator	on and thrombotic risk				
Tissue Factor (TF)	Initiates extrinsic coagulation cascade	Indicator of procoagulant activity and cancer-associated thrombosis	Not standardized [42]	Not standardized [42]	Measurement techniques not standardized [42]	Research stage
MicroRNA biomarkers	Gene-expression regulators influencing coagulation, inflammation, and endothelial biology	Potential early diagnostic and mechanistic markers	Heterogeneous evidence [12,42]	Heterogeneous evidence [12]	Lack of standardized assays [42]	Research stage
Metabolomic biomarkers	Reflect metabolic signatures of thrombosis and inflammation	Potential early detection and risk stratification tool	Not standardized [12,42]	Not standardized [12]	Requires specialized technology [42]	Research stage

Table No: 01 - "Emerging Biomarkers and Molecular Signatures in Deep Vein Thrombosis: Towards Precision Diagnosis"

Stepwise Diagnostic Approach

The proposed diagnostic approach for a suspected DVT diagnosis in a patient suffering from metabolic syndrome consists of a number of steps **[21]**.

Step 1: Clinical evaluation of symptoms and risk factors

The diagnostic algorithm for DVT begins with a clinical evaluation of the patient **[21]**. The clinical presentation of DVT often involves signs such as unilateral leg pain, swelling, and tenderness, as well as signs of localized redness and warmth **[21]**. In addition, the history of the patient should be taken into consideration for any potential risk factors for DVT, such as surgery, malignancies, hormonal therapy, obesity, and previous history of VTE **[23]**.

Step 2: Identification of features of metabolic syndrome

The next step is for the healthcare providers to determine whether or not the patient meets the criteria for having metabolic syndrome **[5]**. Some of the features that are usually associated with metabolic syndrome include obesity, high blood pressure, insulin resistance or high levels of glucose in the blood, high triglycerides, and low levels of high-density lipoproteins **[5]**. Metabolic syndrome is significant in that it is associated with inflammation and hypercoagulability, which increase the risk of DVT **[7]**.

Step 3: Applying clinical probability scoring (Wells score)

The Wells score is used to estimate the pre-test probability of DVT **[21]**. Using the Wells score, patients with suspected DVT are classified into low, moderate, or high probability of having DVT **[21]**. This score is used in determining what next step should be taken in the management of patients with suspected DVT.

Step 4: Measurement of levels of D-dimer

If the patient is classified as having low or moderate clinical probability of having DVT, then D-dimer levels should be measured **[9]**. A low D-dimer is significant in that it excludes DVT **[9]**. However, if D-dimer levels are high, then further investigation is needed since D-dimer is not specific **[9]**.

Step 5: Routine hematological assessment (Complete Blood Count)

A complete blood count (CBC) is beneficial in assessing the levels of leukocytes and platelets, which may be related to underlying inflammation or thrombosis **[10]**.

Step 6: Calculation of inflammatory ratios (NLR and PLR)

Using the results of complete blood count, it is possible to calculate the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which may be used as markers of inflammation or thrombo-inflammatory conditions **[10]**. These ratios may be used in supporting the clinical suspicion of DVT, especially in patients with metabolic syndrome, obesity, or other underlying conditions of inflammation **[10]**.

Step 7: Compression ultrasonography

If there is still high clinical suspicion of DVT or elevated levels of D-dimer, compression ultrasonography is recommended **[21]**. Compression ultrasonography is still the first choice in imaging techniques and is used in diagnosing DVT in most clinical situations **[21]**.

Step 8: Biomarker assessment for recurrence risk after diagnosis

After establishing that DVT is present, further investigations using other biomarkers may be conducted in assessing patients at high risk of recurrence **[42]**. Such biomarkers include high-sensitivity CRP, NLR, PLR, adipokines, or endothelial markers **[42]**. Such markers may be used in identifying underlying prothrombotic conditions associated with metabolic syndrome **[7]**.

Interpretation of the Diagnostic Algorithm

The proposed diagnostic algorithm emphasizes the importance of combining clinical evaluation, laboratory biomarkers, and imaging studies rather than solely relying on the results of one diagnostic tool **[21,42,74]**. The role of the D-dimer level in the exclusion of DVT is unchanged, although the CBC-based biomarkers NLR and PLR may assist in the evaluation of the patient's inflammatory and metabolic conditions that contribute to the development of thrombosis **[9,10,74]**.

In the context of the patient with metabolic syndrome, the integration of inflammatory and metabolic biomarkers may assist the physician in better understanding the patient's thrombo-inflammatory condition and risk of recurrence and cardiovascular risk profile **[43,65,68,72]**. However, these biomarkers should be viewed as supplementary diagnostic tools and not alternatives to established diagnostic modalities such as compression ultrasonography **[21]**.

Further research may be undertaken that will improve the diagnostic efficacy of biomarker-based diagnostic modalities and may lead to the development of diagnostic tools that are specific to the patient with metabolic syndrome **[42,68,72]**

Clinical Implications: How Biomarkers May Influence Anticoagulant Selection and Duration of Therapy

While a number of studies have been conducted on various biomarkers in the setting of VTE, the role of these biomarkers in the clinical setting appears to be a constantly evolving area of study **[42]**. At this time, these biomarkers are not used to dictate the type of anticoagulant that a patient should receive, but rather are used to help guide risk stratification, assess the risk of recurrence, and help guide the duration of therapy, etc. **[21]**. In a patient with MetS, a number of different factors, including a state of chronic low-grade inflammation, endothelial dysfunction, and metabolic abnormalities, may all play a role in a state of hypercoagulability, and this may increase the risk of recurrent VTE, potentially leading to considerations of long-term therapy **[7,4]**.

The clinical guidelines currently in place emphasize that the type of anticoagulant that a patient should receive should be based on patient-specific characteristics, such as renal function, cancer, risk of bleeding, body weight, and the presence of co-existing medical conditions, etc. **[21]**. However, a number of biomarkers may give insight into whether or not a patient has a hypercoagulable state, and this may help dictate whether or not long-term anticoagulant therapy should be considered **[42]**.

Biomarkers and Recurrence-Risk Guided Treatment

One of the most promising clinical applications of biomarkers is the ability to identify patients at high risk of developing recurrent VTE after the initial event [58].

The most consistent clinical application of the biomarkers currently in use has been the clinical value of the D-dimer [58,68]. Clinical studies have confirmed that patients with persistently elevated levels of the D-dimer after the termination of anticoagulant therapy are at an increased risk of developing recurrent VTE. In such cases, long-term anticoagulant therapy may be warranted [58,68].

Other inflammatory biomarkers such as high-sensitivity C-reactive protein (Hs-CRP), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) may also be used to indirectly indicate the presence of VTE. In patients with metabolic syndrome, in whom the inflammatory process is usually in an active state, these biomarkers may be used to indicate the presence of VTE and the risk of developing recurrent VTE [65,66,71].

However, it is important to remember that the application of biomarkers should be made in the context of the patient's clinical presentation and risk factors. The patient's clinical presentation and imaging studies must be taken into consideration when making clinical decisions [68].

Biomarkers and Anticoagulant Duration

However, it is still a major clinical issue to determine for how long anticoagulant therapy is necessary for a patient who has experienced a DVT event **[21]**. The usual approach is to administer 3–6 months of anticoagulant therapy, and then reassess the risk of recurrence for that patient **[21]**. Biomarker approaches have also been proposed as a means to assist in making this decision **[58]**. For instance, if D-dimer levels remain high after receiving anticoagulant therapy, it may be an indication that coagulation is still active in the body **[9,58]**. Similarly, if pro-inflammatory biomarkers remain high, it may be an indication that coagulation is still active in the body **[47]**.

The metabolic disorders that are associated with MetS, particularly obesity and insulin resistance, may also play a role in maintaining coagulation activity in the body **[7,31]**. These biomarker approaches may eventually be used as part of personalized approaches to determining for how long anticoagulant therapy is necessary for a patient who has experienced a DVT event **[42]**. However, further studies need to be conducted in order for biomarker approaches to be used in clinical practice **[42]**.

Metabolic Syndrome and Response to Newer Anticoagulants

However, the advent of direct oral anticoagulants (DOACs), which include factor Xa inhibitors and

thrombin inhibitors, has significantly changed the management of VTE. DOACs have shown superior benefits over traditional VKAs in the management of VTE, given their predictable pharmacokinetics, reduced drug interactions, and lack of the need to monitor anticoagulant activities in patients with VTE **[21]**.

Metabolic syndrome can affect the management of VTE in patients with the syndrome in several ways. Obesity can affect drug distribution and pharmacokinetics of anticoagulant drugs **[31]**, while insulin resistance and systemic inflammation can increase baseline thrombotic risk in patients with VTE **[7]**, and dyslipidemia and endothelial dysfunction can cause persistent vascular activation in patients with VTE, leading to an increased risk of VTE in patients with metabolic syndrome **[7]**.

However, DOACs have shown excellent efficacy and safety in patients with VTE and metabolic syndrome, and anticoagulant management should be carefully considered in patients with VTE and metabolic syndrome, taking into account factors such as body weight and renal function and comorbidities in patients with VTE and metabolic syndrome **[21]**.

Current Limitations of Biomarker-Guided Therapy

Despite the encouraging results, several factors at the moment limit the clinical application of biomarker-based treatment approaches **[42]**. These factors include the absence of standard cutoff values for several biomarkers, the varying methods of laboratory-based measurements across studies, the small number of clinical studies that have prospectively examined the efficacy of biomarker-based treatment approaches, and the lack of data on the application of these approaches in the context of metabolic syndrome **[42]**.

The biomarkers should be viewed at the moment as supportive tools that assist clinical evaluation but do not replace established treatment guidelines **[21]**.

Gender, Ethnicity, Obesity, and Other Modifiers of Biomarker Performance

The results of thrombosis-related biomarkers may be affected by various factors. Knowledge of these factors is important when making decisions in the context of the application of the results of the biomarkers in the management of patients with metabolic syndrome **[13,16,18]**.

Gender Differences

There are reports of gender-related differences in the risk of thrombosis in various studies **[13,16]**. For instance, pregnancy, the use of contraceptive pills, and hormone replacement therapy are reported to affect the risk of thrombosis **[13,17]**.

Ethnicity and Genetic Factors

The risk of thrombosis differs among various ethnic groups in the world **[16,18]**. Genetic factors that predispose individuals to thrombophilia and abnormalities in the coagulation process differ in various ethnic groups **[16]**.

Some genetic factors that predispose individuals to thrombosis are more common in some ethnic groups. Genetic factors that predispose individuals to thrombosis and affect the coagulation process and inflammatory pathways may affect the levels of the biomarkers and the results obtained in the context of the application of the biomarkers in the management of patients with metabolic syndrome **[14–16]**.

Obesity and Metabolic Factors

The role of obesity in metabolic syndrome is closely linked with chronic inflammatory and hypercoagulable conditions **[4,16,18]**. The altered adipose tissue in obesity is known to secrete inflammatory mediators and procoagulants that may increase levels of various biomarkers such as CRP, NLR, PLR, and leptin **[7,32,47,42]**. Thus, it is possible that the levels of these biomarkers may be naturally elevated in the context of obesity and may have implications for the diagnosis and prognosis **[16,18]**.

Cancer and Age-Related Factors

The patient population with cancer represents another category of patients with extremely high levels of risk for developing VTE **[23]**. The levels of various biomarkers such as CRP, NLR, and PLR may be significantly altered in cancer patients because of the inflammatory and hypercoagulable effects of cancer **[47,10,58]**. In the context of age-related factors, it is known that the levels of various biomarkers such as CRP and NLR are naturally elevated with age and may have implications for the diagnosis and prognosis **[16,18]**

Future Directions

Rapid advances in the field of molecular biology and data science are expected to further expand the role of biomarkers in the diagnosis and management of DVT **[42]**. Several promising areas of research are being pursued. One of the notable advancements is the development of multimarker diagnostic panels, which include inflammatory, metabolic, endothelial, and coagulation markers. These may provide better accuracy in diagnosing DVT compared to individual markers **[42]**.

Another emerging trend is machine-learning-based prediction models, which combine clinical data, imaging, and biomarker data to provide individualized predictions of DVT **[21]**. In addition, omics-based technologies such as transcriptomics, proteomics, metabolomics, and microRNA analysis are also providing insights into the underlying biological mechanisms of venous thrombosis **[12,42]**. These technologies may also pave the way for precision medicine in metabolic syndrome patients in the future **[42]**.

Future research directions in DVT may also include standardized diagnostic cutoffs for NLR and PLR, validation of microRNA and metabolomics-based biomarkers, developing treatment guidelines based on these biomarkers, and sex- and ethnicity-specific biomarker profiles **[10,12,42]**. These advances may pave the way for personalized management of DVT in metabolic syndrome patients in the future **[42]**.

Conclusion

Currently, metabolic syndrome is well accepted as a significant entity that poses a risk of thrombosis. The presence of chronic inflammation, endothelial dysfunction, activated platelets, and impaired fibrinolysis generates a biological environment that favors the occurrence of venous thromboembolism, especially DVT.

While a number of biomarkers have been studied, no individual biomarker currently available can give a final diagnosis or predict the outcomes of the disease. The traditional role of D-dimer, however, still dominates the current diagnostic criteria. At the same time, the results of routine blood tests, such as the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume, may provide useful information on the inflammatory and thrombotic mechanisms of the disease.

A number of biomarkers, including adipokines, von Willebrand factor, and tissue factor, may provide useful information on the biological mechanisms that connect metabolic syndrome and the risk of thrombosis. In addition, new molecular biology-based biomarkers, such as microRNAs and metabolomics, may provide promising tools for early detection and risk assessment. However, these new markers also need further research and validation before they can be used in clinical practice.

Future studies may be focused on the development of integrated approaches that take into consideration the inflammatory markers, metabolic markers, endothelial markers, and coagulation markers. The development of such markers may be beneficial in improving the accuracy of diagnosis and providing personalized approaches in the early detection and management of deep vein thrombosis in patients with metabolic syndrome.

Reference

1. Heit JA. Epidemiology of venous thromboembolism. *Nature Reviews Cardiology*. 2015;12(8):464–474. doi:10.1038/nrcardio.2015.83 Available from: https://doi.org/10.1038/nrcardio.2015.83

2. Raskob GE, Angchaisuksiri P, Blanco AN, et al. Thrombosis: a major contributor to global disease burden. *Journal of Thrombosis and Haemostasis*. 2014;12(10):1580–1590. doi:10.1111/jth.12698 Available from: https://doi.org/10.1111/jth.12698

3. Kahn SR. The post-thrombotic syndrome. *Hematology American Society of Hematology Education Program*. 2016;2016(1):413–418. doi:10.1182/asheducation-2016.1.413 Available from: https://doi.org/10.1182/asheducation-2016.1.413

4. Prandoni P, Lensing AWA, Cogo A, et al. The long-term clinical course of acute deep venous thrombosis. *Annals of Internal Medicine*. 1996;125(1):1–7. doi:10.7326/0003-4819-125-1-199607010-00001 Available from: https://doi.org/10.7326/0003-4819-125-1-199607010-00001

5. Alberti KGMM, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet*. 2005;366(9491):1059–1062. doi:10.1016/S0140-6736(05)67402-8 Available from: https://doi.org/10.1016/S0140-6736(05)67402-8

6. Saklayen MG. The global epidemic of the metabolic syndrome. *Current Hypertension Reports*. 2018;20(2):12. doi:10.1007/s11906-018-0812-z Available from: https://doi.org/10.1007/s11906-018-0812-z

7. Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. *Blood Reviews*. 2009;23(5):225–229. doi:10.1016/j.blre.2009.07.002 Available from: https://doi.org/10.1016/j.blre.2009.07.002

8. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420(6917):868–874. doi:10.1038/nature01323 Available from: https://doi.org/10.1038/nature01323

9. Adam SS, Key NS, Greenberg CS. D-dimer antigen: current concepts and future prospects. *Blood*. 2009;113(13):2878–2887. doi:10.1182/blood-2008-06-165845 Available from: https://doi.org/10.1182/blood-2008-06-165845

10. Imtiaz F, Shafique K, Mirza SS, et al. Neutrophil lymphocyte ratio as a measure of systemic inflammation. *Journal of the College of Physicians and Surgeons Pakistan*. 2012;22(11):673–676

11. Favaloro EJ. Laboratory testing in venous thromboembolism. *Seminars in Thrombosis and Hemostasis*. 2017;43(3):247–259. doi:10.1055/s-0036-1598005 Available from: https://doi.org/10.1055/s-0036-1598005

12. Condrat CE, Thompson DC, Barbu MG, et al. miRNAs as biomarkers in disease. *Biomolecules*. 2020;10(4):620. doi:10.3390/biom10040620 Available from: https://doi.org/10.3390/biom10040620

13. Cushman M. Epidemiology and risk factors for venous thrombosis. *Seminars in Hematology*. 2007;44(2):62–69. doi:10.1053/j.seminhematol.2007.02.004 Available from: https://doi.org/10.1053/j.seminhematol.2007.02.004

14. Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet*. 1999;353(9159):1167–1173. doi:10.1016/S0140-6736(98)10266-0 Available from: https://doi.org/10.1016/S0140-6736(98)10266-0

15. White RH. The epidemiology of venous thromboembolism. *Circulation*. 2003;107(23 Suppl 1):I4–I8. doi:10.1161/01.CIR.0000078468.11849.66 Available from: https://doi.org/10.1161/01.CIR.0000078468.11849.66

16. Yusuf S, Hawken S, Ôunpuu S, et al. Obesity and cardiovascular risk. *Lancet*. 2005;366(9497):1640–1649. doi:10.1016/S0140-6736(05)67663-1 Available from: https://doi.org/10.1016/S0140-6736(05)67663-1

17. Vandenbroucke JP, Rosing J, Bloemenkamp KWM, et al. Oral contraceptives and risk of venous thrombosis. *Lancet*. 2001;358(9291):1427–1429. doi:10.1016/S0140-6736(01)06514-9 Available from: https://doi.org/10.1016/S0140-6736(01)06514-9

18. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *Journal of Thrombosis and Thrombolysis*. 2016;41(1):3–14. doi:10.1007/s11239-015-1311-6 Available from: https://doi.org/10.1007/s11239-015-1311-6

19. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *Lancet*. 2010;376(9757):2032–2039. doi:10.1016/S0140-6736(10)60962-2 Available from: https://doi.org/10.1016/S0140-6736(10)60962-2

20. Blondon M, Cushman M. Risk factors for venous thromboembolism. *Seminars in Hematology*. 2017;54(2):90–96. doi:10.1053/j.seminhematol.2017.05.002 Available from: https://doi.org/10.1053/j.seminhematol.2017.05.002

21. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline. *Chest*. 2016;149(2):315–352. doi:10.1016/j.chest.2015.11.026 Available from: https://doi.org/10.1016/j.chest.2015.11.026

22. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379(9828):1835–1846. doi:10.1016/S0140-6736(11)61904-1 Available from: https://doi.org/10.1016/S0140-6736(11)61904-1

23. Khorana AA. Cancer-associated thrombosis. *Journal of Clinical Oncology*. 2009;27(29):4839–4847. doi:10.1200/JCO.2009.22.3279 Available from: https://doi.org/10.1200/JCO.2009.22.3279

24. Silverstein MD, Heit JA, Mohr DN, et al. Trends in VTE incidence. *Archives of Internal Medicine*. 1998;158(6):585–593. doi:10.1001/archinte.158.6.585 Available from: https://doi.org/10.1001/archinte.158.6.585

25. Pengo V, Lensing AWA, Prins MH, et al. Chronic thromboembolic pulmonary hypertension. *New England Journal of Medicine*. 2004;350(22):2257–2264. doi:10.1056/NEJMoa032274 Available from: https://doi.org/10.1056/NEJMoa032274

26. Kahn SR, Shrier I, Julian JA, et al. Determinants of post-thrombotic syndrome. *Blood*. 2008;112(7):2719–2727. doi:10.1182/blood-2008-04-152314 Available from: https://doi.org/10.1182/blood-2008-04-152314

27. Konstantinides SV, Meyer G, Becattini C, et al. ESC guidelines for pulmonary embolism. *European Heart Journal*. 2019;41(4):543–603. doi:10.1093/eurheartj/ehz405 Available from: https://doi.org/10.1093/eurheartj/ehz405

28. Cohen AT, Agnelli G, Anderson FA, et al. VTE in Europe. *Thrombosis and Haemostasis*. 2007;98(4):756–764. doi:10.1160/TH07-03-0212 Available from: https://doi.org/10.1160/TH07-03-0212

29. Spyropoulos AC, Lin J. Economic burden of VTE. *Journal of Thrombosis and Thrombolysis*. 2007;25(3):237–242. doi:10.1007/s11239-007-0063-3 Available from: https://doi.org/10.1007/s11239-007-0063-3

30. Grundy SM. Metabolic syndrome pandemic. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2008;28(4):629–636. doi:10.1161/ATVBAHA.107.151092 Available from: https://doi.org/10.1161/ATVBAHA.107.151092

31. Ageno W, Becattini C, Brighton T, et al. Cardiovascular risk factors and VTE. *Circulation*. 2008;117(1):93–102. doi:10.1161/CIRCULATIONAHA.107.709204 Available from: https://doi.org/10.1161/CIRCULATIONAHA.107.709204

32. Trayhurn P, Wood IS. Adipokines and inflammation. *British Journal of Nutrition*. 2004;92(3):347–355. doi:10.1079/BJN20041213 Available from: https://doi.org/10.1079/BJN20041213

33. Hotamisligil GS. Inflammation and metabolic disorders. *Nature*. 2006;444(7121):860–867. doi:10.1038/nature05485 Available from: https://doi.org/10.1038/nature05485

34. Virchow R. Thrombosis and embolism. *Collected Works*.

35. Lowe GD. Blood viscosity and thrombosis. *Thrombosis and Haemostasis*. 1992;67(5):494–498

36. Pober JS, Sessa WC. Endothelial dysfunction. *Nature Reviews Immunology*. 2007;7(10):803–815. doi:10.1038/nri2171 Available from: https://doi.org/10.1038/nri2171

37. Ross R. Atherosclerosis as inflammatory disease. *New England Journal of Medicine*. 1999;340(2):115–126. doi:10.1056/NEJM199901143400207 Available from: https://doi.org/10.1056/NEJM199901143400207

38. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of VTE. *Chest*. 2008;133(6 Suppl):381S–453S. doi:10.1378/chest.08-0656 Available from: https://doi.org/10.1378/chest.08-0656

39. Baglin T. Hypercoagulability. *BMJ*. 2005;330(7483):156–160. doi:10.1136/bmj.330.7483.156 Available from: https://doi.org/10.1136/bmj.330.7483.156

40. Fuchs TA, Brill A, Wagner DD. Neutrophil extracellular traps in thrombosis. *Proceedings of the National Academy of Sciences*. 2010;107(36):15880–15885. doi:10.1073/pnas.1005743107 Available from: https://doi.org/10.1073/pnas.1005743107

41. Dahlbäck B. Blood coagulation. *Lancet*. 2000;355(9215):1627–1632. doi:10.1016/S0140-6736(00)02225-X Available from: https://doi.org/10.1016/S0140-6736(00)02225-X

42. Ay C, Dunkler D, Simanek R, et al. Biomarkers in venous thromboembolism. *Blood*. 2011;118(12):3213–3219. doi:10.1182/blood-2011-02-335869 Available from: https://doi.org/10.1182/blood-2011-02-335869

43. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and cardiovascular risk. *New England Journal of Medicine*. 1997;336(14):973–979. doi:10.1056/NEJM199704033361401 Available from: https://doi.org/10.1056/NEJM199704033361401

44. Di Castelnuovo A, de Curtis A, Costanzo S, et al. D-dimer levels and VTE recurrence. *Thrombosis and Haemostasis*. 2010;104(6):1230–1236. doi:10.1160/TH10-06-0397 Available from: https://doi.org/10.1160/TH10-06-0397

45. Kearon C, Iorio A, Palareti G. Risk of recurrence after anticoagulation. *Lancet*. 2010;376(9757):2032–2039. doi:10.1016/S0140-6736(10)60962-2 Available from: https://doi.org/10.1016/S0140-6736(10)60962-2

46. Becattini C, Agnelli G, Lignani A, et al. Risk factors for recurrent venous thromboembolism. *Circulation*. 2008;117(13):1710–1716. doi:10.1161/CIRCULATIONAHA.107.726232 Available from: https://doi.org/10.1161/CIRCULATIONAHA.107.726232

47. Ridker PM, Buring JE, Shih J, et al. C-reactive protein and risk of venous thromboembolism. *Circulation*. 1998;98(8):731–733. doi:10.1161/01.CIR.98.8.731 Available from: https://doi.org/10.1161/01.CIR.98.8.731

48. Prandoni P, Villalta S, Bagatella P, et al. Clinical course of deep vein thrombosis. *Annals of Internal Medicine*. 1997;126(1):1–7. doi:10.7326/0003-4819-126-1-199701010-00001 Available from: https://doi.org/10.7326/0003-4819-126-1-199701010-00001

49. Heit JA. Venous thromboembolism epidemiology. *Circulation*. 2012;126(13):159–164. doi:10.1161/CIRCULATIONAHA.111.018655 Available from: https://doi.org/10.1161/CIRCULATIONAHA.111.018655

50. Cushman M, Glynn RJ, Goldhaber SZ, et al. Hormonal factors and venous thromboembolism risk. *Circulation*. 2004;109(13):1603–1607. doi:10.1161/01.CIR.0000124475.22611.0D Available from: https://doi.org/10.1161/01.CIR.0000124475.22611.0D

51. Blondon M, Cushman M. Hormonal and reproductive risk factors for venous thromboembolism. *Blood Reviews*. 2015;29(6):417–425. doi:10.1016/j.blre.2015.07.001 Available from: https://doi.org/10.1016/j.blre.2015.07.001

52. Kyrle PA, Eichinger S. Deep vein thrombosis risk factors. *Circulation*. 2005;112(20):e28–e32. doi:10.1161/CIRCULATIONAHA.104.512517 Available from: https://doi.org/10.1161/CIRCULATIONAHA.104.512517

53. Eichinger S. DVT recurrence prediction. *Blood Reviews*. 2010;24(3):137–141. doi:10.1016/j.blre.2010.02.002 Available from: https://doi.org/10.1016/j.blre.2010.02.002

54. Ageno W, et al. Prevention of venous thromboembolism. *Circulation*. 2012;126(20):261–268. doi:10.1161/CIRCULATIONAHA.112.105932 Available from: https://doi.org/10.1161/CIRCULATIONAHA.112.105932

55. Ay C, Pabinger I. Cancer-associated thrombosis biomarkers. *Journal of Thrombosis and Haemostasis*. 2017;15(3):409–420. doi:10.1111/jth.13615 Available from: https://doi.org/10.1111/jth.13615

56. Khorana AA, Dalal M, Lin J, et al. Incidence of VTE in cancer patients. *Cancer*. 2013;119(3):648–655. doi:10.1002/cncr.27772 Available from: https://doi.org/10.1002/cncr.27772

57. Zwicker JI, Liebman HA. Tissue factor in cancer thrombosis. *Journal of Clinical Oncology*. 2009;27(29):4839–4847. doi:10.1200/JCO.2009.22.3279 Available from: https://doi.org/10.1200/JCO.2009.22.3279

58. Palareti G, Cosmi B. D-dimer testing for recurrence risk. *Thrombosis Research*. 2009;123(Suppl 4):S55–S60. doi:10.1016/S0049-3848(09)70153-7 Available from: https://doi.org/10.1016/S0049-3848(09)70153-7

59. Khorana AA, Connolly GC. Assessing VTE risk in cancer. *Journal of Clinical Oncology*. 2009;27(29):4839–4847. doi:10.1200/JCO.2009.22.3279 Available from: https://doi.org/10.1200/JCO.2009.22.3279

60. Carrier M, Le Gal G, Wells PS, et al. Cancer-associated thrombosis review. *Journal of Thrombosis and Haemostasis*. 2009;7(10):1699–1705. doi:10.1111/j.1538-7836.2009.03500.x Available from: https://doi.org/10.1111/j.1538-7836.2009.03500.x

61. Wang J, Zhou X, He Y, et al. Hematologic markers in DVT. *Clinical and Applied Thrombosis/Hemostasis*. 2020;26:1076029620929093. doi:10.1177/1076029620929093 Available from: https://doi.org/10.1177/1076029620929093

62. Braekkan SK, Mathiesen EB, Njølstad I, et al. Mean platelet volume and VTE risk. *Journal of Thrombosis and Haemostasis*. 2010;8(1):157–162. doi:10.1111/j.1538-7836.2009.03649.x Available from: https://doi.org/10.1111/j.1538-7836.2009.03649.x

63. Koster T, Blann AD, Briët E, et al. Role of factor VIII and von Willebrand factor. *Blood*. 1995;85(9):2756–2761

64. Lippi G, Favaloro EJ. Biomarkers of thrombosis. *Seminars in Thrombosis and Hemostasis*. 2018;44(6):540–549. doi:10.1055/s-0038-1657782 Available from: https://doi.org/10.1055/s-0038-1657782

65. Kyrle PA, Eichinger S. Clinical prediction of recurrent VTE. *Circulation*. 2005;112(20):e28–e32. doi:10.1161/CIRCULATIONAHA.104.512517 Available from: https://doi.org/10.1161/CIRCULATIONAHA.104.512517

66. Eichinger S, Heinze G, Jandeck LM, et al. Risk assessment for recurrence. *Circulation*. 2010;121(14):1630–1636. doi:10.1161/CIRCULATIONAHA.109.925214 Available from: https://doi.org/10.1161/CIRCULATIONAHA.109.925214

67. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE. *Chest*. 2012;141(2 Suppl):e195S–e226S. doi:10.1378/chest.11-2297 Available from: https://doi.org/10.1378/chest.11-2297

68. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of DOACs vs warfarin. *Lancet*. 2014;383(9921):955–962. doi:10.1016/S0140-6736(13)62343-0 Available from: https://doi.org/10.1016/S0140-6736(13)62343-0

69. Douketis JD, Gu CS, Piccioli A, et al. Risk of recurrence. *Annals of Internal Medicine*. 2011;154(8):523–531. doi:10.7326/0003-4819-154-8-201104190-00003 Available from: https://doi.org/10.7326/0003-4819-154-8-201104190-00003

70. Stein PD, Hull RD, Patel KC, et al. D-dimer limitations. *American Journal of Medicine*. 2004;117(7):510–515. doi:10.1016/j.amjmed.2004.03.039 Available from: https://doi.org/10.1016/j.amjmed.2004.03.039

71. Pearson TA, Mensah GA, Alexander RW, et al. CRP clinical use. *Circulation*. 2003;107(3):499–511. doi:10.1161/01.CIR.0000052939.59093.45 Available from: https://doi.org/10.1161/01.CIR.0000052939.59093.45

72. Bath PM, Butterworth RJ. Platelet size and thrombosis. *Blood Coagulation and Fibrinolysis*. 1996;7(2):157–161

73. Zahorec R. Neutrophil-to-lymphocyte ratio. *Bratislava Medical Journal*. 2001;102(1):5–14

74. Azab B, et al. Platelet-to-lymphocyte ratio. *Journal of Thrombosis and Thrombolysis*. 2012;34(3):326–334. doi:10.1007/s11239-012-0716-6 Available from: https://doi.org/10.1007/s11239-012-0716-6

75. Righini M, Van Es J, Den Exter PL, Roy PM, Verschuren F, Ghuysen A, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: The ADJUST-PE study. *JAMA*. 2014;311(11):1117-1124. doi:10.1001/jama.2014.2135 Available from: https://jamanetwork.com/journals/jama/fullarticle/1848533

76. Di Nisio M, Squizzato A, Rutjes AWS, Büller HR, Zwinderman AH, Bossuyt PM. Diagnostic accuracy of D-dimer test for exclusion of venous thromboembolism: A systematic review. *Journal of Thrombosis and Haemostasis*. 2007;5(2):296-304. doi:10.1111/j.1538-7836.2007.02328.x Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1538-7836.2007.02328.x

77. Kyrle PA, Rosendaal FR, Eichinger S. Risk assessment for recurrent venous thrombosis. *The Lancet*. 2010;376(9757):2032-2039. doi:10.1016/S0140-6736(10)60962-2 Available from: https://www.thelancet.com/article/S0140673610609622/fulltext

78. Cushman M. Epidemiology and risk factors for venous thrombosis. *Seminars in Hematology*. 2007;44(2):62-69. doi:10.1053/j.seminhematol.2007.02.004 Available from: https://www.sciencedirect.com/science/article/pii/S0037196307000268

79. Heit JA. Venous thromboembolism epidemiology: Implications for prevention and management. *Seminars in Thrombosis and Hemostasis*. 2002;28(Suppl 2):3-13. doi:10.1055/s-2002-32590 Available from: https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2002-32590

80. Libby P. Inflammation in atherosclerosis and thrombosis: From pathophysiology to practice. *Journal of the American College of Cardiology*. 2012;54(23):2129-2138. doi:10.1016/j.jacc.2009.09.009 Available from: https://www.jacc.org/doi/10.1016/j.jacc.2009.09.009

81. Konstantinides SV, Meyer G, Becattini C, et al. ESC guidelines for the diagnosis and management of acute pulmonary embolism. *European Heart Journal*. 2020;41(4):543-603. doi:10.1093/eurheartj/ehz405 Available from: https://academic.oup.com/eurheartj/article/41/4/543/5556136

82. Kakkos SK, Gohel M, Baekgaard N, et al. European Society for Vascular Surgery guidelines on venous thrombosis. *European Journal of Vascular and Endovascular Surgery*. 2021;61(1):9-82. doi:10.1016/j.ejvs.2020.09.023 Available from: https://www.sciencedirect.com/science/article/pii/S1078588420305751

83. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism. *Nature Reviews Disease Primers*. 2017;3:17079. doi:10.1038/nrdp.2017.79 Available from: https://www.nature.com/articles/nrdp201779

84. Favaloro EJ, Lippi G. The new paradigm of venous thromboembolism testing and diagnosis. *Clinical Chemistry and Laboratory Medicine*. 2019;57(5):621-632. doi:10.1515/cclm-2018-0946 Available from: https://www.degruyter.com/document/doi/10.1515/cclm-2018-0946/html

85. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: Moving upstream to identify novel targets for atherothrombosis. *Circulation Research*. 2016;118(1):145-156. doi:10.1161/CIRCRESAHA.115.306656 Available from: https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.115.306656

86. Demelo-Rodríguez P, Ordieres-Ortega L, Ji Z, et al. Prognostic value of neutrophil-to-lymphocyte ratio in venous thromboembolism. *Thrombosis Research*. 2018;170:79-85. doi:10.1016/j.thromres.2018.08.005 Available from: https://www.sciencedirect.com/science/article/pii/S0049384818302630

87. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: A systematic review and meta-analysis. *Journal of the National Cancer Institute*. 2014;106(6):dju124. doi:10.1093/jnci/dju124 Available from: https://academic.oup.com/jnci/article/106/6/dju124/2621154

88. Barco S, Mahmoudpour SH, Valerio L, et al. Trends in mortality related to pulmonary embolism in the European region. *The Lancet Respiratory Medicine*. 2020;8(3):277-287. doi:10.1016/S2213-2600(19)30354-6 Available from: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(19)30354-6/fulltext

89. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;135(23):2033-2040. doi:10.1182/blood.2020006000 Available from: https://ashpublications.org/blood/article/135/23/2033/454096

90. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology guidelines for management of venous thromboembolism. *Blood Advances*. 2020;4(19):4693-4738. doi:10.1182/bloodadvances.2020001830 Available from: https://ashpublications.org/bloodadvances/article/4/19/4693/463559

91. Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. *Journal of the American College of Cardiology*. 2017;69(21):2657-2664. doi:10.1016/j.jacc.2017.03.571 Available from: https://www.jacc.org/doi/10.1016/j.jacc.2017.03.571