Hypercoagulable State in COPD

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Chronic Obstructive Pulmonary Disease (COPD) is a chronic inflammatory disease with multisystemic manifestations. Studies either held on stable disease patients or during exacerbations, have demonstrated that COPD is strongly related to venous thromboembolism and cardiovascular events.

hypercoagulability   coagulation factors   stable COPD

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic debilitating lung disease with a high prevalence of approximately 380 million cases worldwide [1]. It is currently the third leading cause of death, responsible for approximately 6% of the world's total deaths (approximately 3.3 million annually) [2]. In addition to the known devastating respiratory consequences, a large number of studies support the hypothesis that COPD increases the risk for both venous thromboembolism (VTE) and cardiovascular disease (CVD). Thus, patients with COPD exhibit an enhanced risk of pulmonary embolism and deep vein thrombosis compared to randomly matched COPD-free subjects [3], and are also more likely to be diagnosed with cardiovascular disease compared with non-COPD subjects, having nearly 2.5 times the risk of CVD [4]. Although the observed association of COPD with CVD and VTE can be partially explained by comorbidities and shared risk factors, there is strong evidence that COPD increases the risk for cardiovascular morbidity and mortality independently of age, gender, and smoking history [5] [6]. It is of note that up to 63.5% of patients with COPD die of comorbid circulatory system diseases [7].

Increased thrombin formation [8], reflected by elevated thrombin–antithrombin complexes [9], tissue factor procoagulant activity [10] and activated factor XI [11], increased d-dimers [12], and FI [13], FII and FX [14] levels in the serum of COPD patients support the theory that a hypercoagulable state occurs in patients with COPD and might contribute to the incidence of atherothrombotic events and VTE, increasing disease related morbidity and mortality. Pulmonary embolism accounts for approximately 10% of deaths in patients with stable COPD, on long term oxygen therapy (LTOT) [15]. Kim et al., demonstrated that BMI, exercise capacity, and medical comorbidities were significantly associated with VTE in moderate to severe COPD and that physicians should suspect VTE in patients who present with dyspnea and should consider possibilities other than infection as causes of COPD exacerbation [16].

Potential pathways illustrating pathogenetic mechanisms of increased risk of CVD and VTE in COPD are imprecise. Evidence illustrates four possible synergistic mechanisms: systemic inflammation [17], platelet activation [18], oxidative stress [19], and hypoxia, either sustained in severe COPD or intermittent during exercise and sleep [20]

[21]. COPD is a disease where both local and systemic inflammation is present [17]. Prolonged systemic inflammation in COPD is indicated by increased serum concentrations of inflammatory markers such as fibrinogen, C-reactive protein (CRP), interleukin 6, interleukin 8, and TNF-a [22]. The inflammatory response and the activation of coagulation are two important mechanisms of a host's defense response against infection that do not work independently, but conjointly in an intricate and synchronous process [23]. Several investigators have suggested that low-grade inflammation in COPD largely contributes to a prothrombotic state [24]. Platelets serve a crucial role in hemostasis and inflammation [18]. Activated platelets produce several prothrombotic factors that also act as inflammatory signals, such as platelet factor 4, plasminogen activator inhibitor (PAI-1), von Willebrand factor (vWF), and fibrinogen [25]. Platelets also secrete soluble *P*-selectin and CD40L, which serve a dual purpose of promoting thrombus formationand activating inflammatory cells [23]. Platelet *P*-selectin has been shown to bind PSGL-1 on leukocytes to promote fibrin degradation and tissue factor release.

Oxidative stress is triggered by reactive oxygen species, predisposing to thrombosis by impairing red blood cells' quality and function [26], inducing endothelial dysfunction and injury, and activating leukocytes, consequently affecting the clotting system [19][27]. Oxidative stress also elevates reactive oxygen species within platelets that can augment platelet activation and thrombotic susceptibility [18]. Mechanisms by which hypoxia can stimulate a prothrombotic response include platelet activation and hypoxia-inducible transcription factors (HIFs) mediated or HIF-independent increase in procoagulant factors or reduction of coagulation inhibitors [28]. Hypoxia can also induce PAI-1 in a time-dependent process; by enhancing TF and repressing tissue factor pathway inhibitor (TFPI) transcript expression [29], decreasing protein S levels and increasing thrombin generation, it contributes to the prothrombotic effect [30].

COPD patients are at heightened risk of VTE during acute exacerbations of COPD (AECOPD) [31][32], which may be due to clotting system activation [33]. AECOPDs, which are crucial events in the disease's natural history, can concomitantly lead to hypoxia and amplification of systemic inflammation, thus magnifying the prothrombotic state [34]. Respiratory tract infections, the most frequent trigger of AECOPD, represent a transient risk factor for VTE [35]. In a population-based case-control study in Northern Denmark, the Incidence Rate Ratio (IRR) for VTE within the first 3 months after infection was 12.5 (95% CI: 11.3–13.9) for patients with hospital-diagnosed infection and 4.0 (95% CI: 3.8–4.1) for patients treated with antibiotics in the community, compared with individuals without infection during the year before VTE [36]. Immobilization is another factor, existent during AECOPD, which imposes an even greater risk for VTE [37][38].

Obstructive sleep apnea (OSA) is a frequently encountered comorbidity among COPD patients. The estimated prevalence of sleep disturbance in COPD varies from 34% to 78% [39][40]. OSA further magnifies the risk of VTE through hypoxia, systemic inflammation, endothelial damage, and connection to metabolic syndrome [41][42]. Xie et al., demonstrated that patients with COPD and OSA had higher odds of PE compared to control patients (individuals without OSA or COPD), with significance persisting after adjusting for covariates (OR 5.66; 95%CI 1.80–16.18, *p* = 0.004). Interestingly, patients with COPD and OSA had significantly higher odds of PE compared with those with isolated OSA in adjusted models (OR 3.89; 95%CI 1.27–10.68, *p* = 0.019) [43].

Altered coagulation mechanisms in COPD affect danger for cardiovascular events as well; there is evidence linking coagulation and risk of cardiovascular disease, including the presence of several coagulation factors within the atherosclerotic lesions [44]; animal studies indicating accelerated atherosclerosis in animals with a hypercoagulable genotype [45]; associations between hypercoagulability-related hemostatic gene variants and cardiovascular disease [46]; and associations of elevated hemostatic factor levels with arterial thrombosis, cardiovascular disease stemmed from the presence of coagulation factors in atherosclerotic lesions [44].

2. An Overview of the Coagulation Mechanism

The progress of coagulation can be generally divided into the following stages: initiation, amplification, propagation, and stabilization [47]. The mechanism of hemostasis is an intricate process which is generated through a series of clotting factors. The coagulation cascade of secondary hemostasis has two initial pathways which lead to fibrin formation and the intrinsic and the extrinsic pathway. The intrinsic pathway consists of factors I (fibrinogen), II (prothrombin), IX, X, XI, and XII. The extrinsic pathway involves factors I, II, VII, and X. The common pathway comprises factors I, II, V, VIII, X. The two pathways are a series of reactions in which coagulation factors that circulate as zymogens (inactive enzyme precursor) of a serine protease and its glycoprotein co-factors, are activated to become active components which then catalyze the next reaction in the cascade, ultimately resulting in activation of fibrinogen and formation of cross-linked fibrin. Factors II, VII, IX, X, XI and XII are serine proteases, whereas factors V, VIII are glycoproteins, and XIII is a transglutaminase. Fibrinogen, factors II, V, VII, VIII, IX, X, XI, XIII, and protein C and S are synthesized by the liver, while factor VII is created by the vascular endothelium [48].

A summary of the coagulation cascade is presented in **Figure 1**.
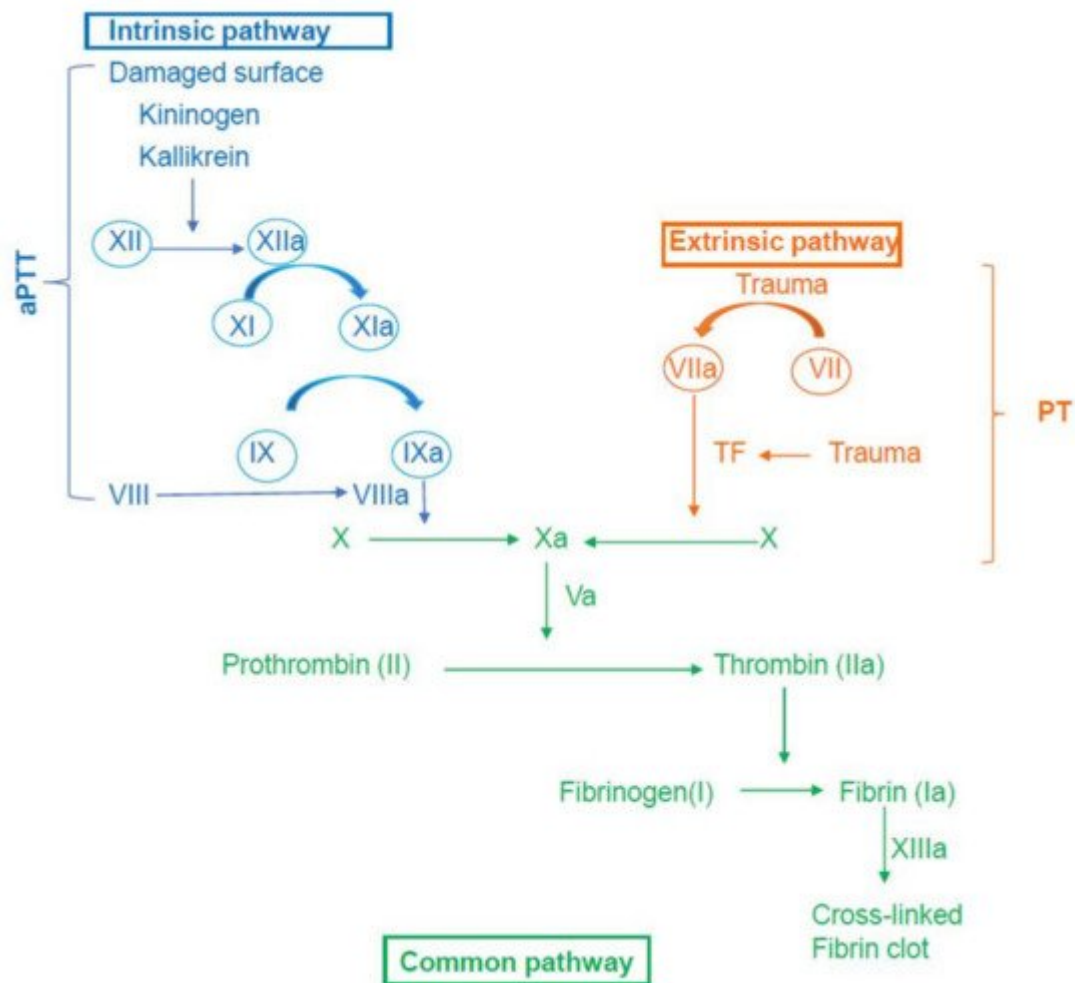
Figure 1. Summary of the coagulation cascade. aPTT: activated Partial Thromboplastin Time; PT: Prothrombin Time; TF: Tissue Factor.

3. Hypercoagulability in Stable COPD

COPD is a common comorbidity or risk factor for venous thromboembolism (VTE). Both clinical and basic research has linked smoking and COPD to abnormalities of coagulation and fibrinolysis and to VTE [49]. In a 5451-patient DVT registry, in 668 individuals (12.3%) COPD was present as comorbidity [50]. 36,949 consecutive patients over 18 years with acute, symptomatic, objectively confirmed VTE were enrolled in the RIETE study. Of these, 4036 (10.9%) had COPD, of whom 2452 (61%) initially presented with PE and 1584 (39%) presented with DVT [51].

Studies conducted on stable COPD patients, have demonstrated a significant increase of coagulation factors levels. In the third National Health and Nutrition Examination Survey (NHANES III), with a total study sample size of 15,697 adults, of whom 2366 had COPD, fibrinogen levels were higher in COPD patients compared to subjects without COPD, and were associated with GOLD spirometric stages [52]. Similarly, Garcia-Rio et al., demonstrated that fibrinogen was higher in patients with COPD compared to control subjects, however fibrinogen levels were not associated with disease severity (as expressed by GOLD spirometric groups or BODE index) [53]. In the study by Eickhoff et al., fibrinogen levels were significantly higher in stable COPD patients compared to COPD-free subjects

[54]. Samareh et al., demonstrated that fibrinogen levels were higher among COPD patients compared to controls; however, no statistical significance or any correlation between fibrinogen and severity of the disease was detected [55]. Agale et al., conducted a study on stable COPD patients and compared them with healthy subjects, demonstrating that fibrinogen levels are higher among COPD patients and that they correlate directly with COLD COPD groups [56]. These 5 studies demonstrate that fibrinogen levels are higher in COPD patients compared to control subjects and are associated with disease severity.

Arregui et al., observed that COPD patients had higher fibrinogen, D-dimer, factor VIII, von Willebrand factor (vWF) Ag, and vWF Ac compared with healthy individuals [57]. In another study by Zhang et al., D-dimer and fibrinogen levels were higher in stable COPD patients compared to healthy subjects [12]. In a small study, Polatli et al., examined the levels of fibrinogen, vWF, and microalbuminuria between 33 stable COPD patients, 26 patients with AECOPD and 16 control subjects. Patients with stable COPD had higher levels of fibrinogen compared to healthy subjects, while vWF and microalbuminuria did not differ significantly between the 2 groups. Patients with AECOPD had further elevated levels of fibrinogen and vWF compared to patients with stable COPD, while microalbuminuria did not differ significantly between the 2 groups [58]. These 3 studies demonstrate that COPD patients exhibit higher D-dimer, factor VIII, and vWF levels compared to control subjects, while fibrinogen, D-dimer, and vWF levels are further amplified during exacerbation.

In a study from our group, stable COPD patients had higher levels of D-dimer, fibrinogen, FII, FV, FVIII, FX, and lower levels of protein S and AT compared to COPD-free control subjects. Moreover, FII was negatively associated with FEV1 and age; FV and FX were negatively associated with FEV1; D-dimers were positively associated with pack-years and negatively associated with DLCO; fibrinogen was positively associated with CRP; FVIII was positively associated with blood neutrophil count; Protein S was positively associated with CRP and negatively associated with age and CAT score; and AT was negatively associated with blood neutrophil count, CRP and age [59]. In this study, patients with stable COPD exhibited increased levels of key coagulation factors and decreased levels of coagulation inhibitors compared to COPD-free smokers, indicating a prothrombotic state in stable COPD. Among COPD patients, FII, FV, FX, and D-dimers were associated with COPD severity; fibrinogen, FVIII, Protein S, and antithrombin were associated with inflammatory markers, whereas FII and FX were associated with LDL levels. Undas et al., detected that COPD patients had elevated fibrinogen, FII, FV, FVII, FVIII, and FIX, lower free TFP, higher total thrombin levels and higher maximum thrombin levels, compared with controls [14]. In a study with very interesting findings including 60 COPD patients with stable disease, FXIa was detected in 9 (15%) and TF activity in 7 (11.7%) COPD patients. Those patients had higher prothrombin fragment 1.2, IL-6 and CRP, thus associating COPD to hypercoagulability and chronic systemic inflammation [11]. Those 3 studies illustrated that COPD patients exhibit elevated coagulation factors and inflammatory markers compared to control subjects, featuring systemic inflammation as a possible mechanism of hypercoagulability.

Similar findings were observed for TF procoagulant activity and TAT levels in COPD patients compared to control subjects, indicating enhanced thrombin generation [60]. In a study by Ashitani et al., plasma levels of TAT complex, fibrinopeptide-A, tissue plasminogen activator-plasminogen activator inhibitor (tPA-PAI), and 3-thromboglobulin, a marker of platelet activation, were significantly higher in stable COPD patients compared to healthy never-smokers

controls [8]. In the study by Szczypiorska et al., significantly higher concentrations of TF and TF pathway inhibitor (TFPI) and fibrinogen, were observed in patients with COPD. Likewise, aPTT was shortened in COPD patients compared with the control group [61]. Cella et al., compared the levels of nitric oxide (a powerful vasodilator and inhibitor of platelets aggregation), thrombomodulin (the endothelial surface site for binding and deactivating thrombin that subsequent activates protein C), and TFPI between patients with COPD and healthy controls, to evaluate the endothelial cell dysfunction associated with COPD. Both nitric oxide and thrombomodulin levels were significantly decreased in COPD patients compared to control subjects. Patients with COPD showed a significantly higher TFPI antigen plasma level than controls [62]. In the study by Waschki et al., PAI was enhanced inCOPD patients compared with COPD-free control subjects, with the highest levels observed in GOLD COPD stage II and III [63]. The 5 aforementioned studies provide evidence that TF, TFPI, TAT, tPA-PAI, and thrombomodulin levels were significantly enhanced in stable COPD patients compared to healthy controls.

4. Hypercoagulability during COPD exacerbations

The risk of VTE during acute exacerbations of COPD appears to be significant [64]. In 1144 patients with COPD admitted to hospital with acute exacerbation, the VTE rate was 6.8% (78 patients). This could be underestimated due to the poor sensitivity of ultrasound for asymptomatic DVT [65]. This study excluded patients with previous thromboembolism, cancer, or heart failure, suggesting that COPD itself, or the concurrent reduced mobility, play important roles in vulnerability to VTE. Furthermore Kim et al., demonstrated that higher fibrinogen levels (>350 mg/dL) were associated with frequent exacerbations and COPD severity [66].

In the study by Saldias et al., fibrinogen levels of COPD patients were examined at stable phase and during AECOPD and were significantly higher during AECOPD. Interestingly, fibrinogen levels were reduced 15 and 30 days after AECOPD, nevertheless still remained higher than levels at stable phase [67]. In another study, fibrinogen levels of AECOPD patients were compared to convalescence values, 40 days after exacerbation, and were found to be significantly higher during AECOPD [68]. Similarly, in the study by Valipour et al., fibrinogen levels of stable COPD patients were significantly higher compared to those of healthy controls. Furthermore, fibrinogen levels of patients with AECOPD were significantly higher compared to convalescence values (6 weeks after AECOPD) and to those of the healthy controls [69]. Moreover, in the study by Wedzicha et al., including patients with COPD, the plasma fibrinogen levels were elevated during exacerbation compared to baseline values [34]. Thomas and Yuvarajan, examined fibrinogen levels in patients with stable COPD, patients with AECOPD and control subjects. Stable COPD patients exhibited higher levels compared to healthy subjects. Moreover, fibrinogen levels were further increased during exacerbation compared to stable COPD patients. Among COPD patients, fibrinogen was significantly associated with severity of obstruction [70]. These 5 studies illustrate that fibrinogen levels are elevated during AECOPD compared either to convalescence values or healthy subjects.

Maclay et al., compared the levels of fibrinogen and platelet-monocyte aggregates (a sensitive marker of platelet activation which is raised in patients with acute coronary syndromes, smokers, and in those with rheumatoid arthritis) between patients with stable COPD and healthy controls, detecting significantly higher levels among COPD patients of both fibrinogen and platelet-monocyte aggregates. D-dimer levels did not differ significantly

between the two groups. Subsequently, platelet-monocyte aggregates of 12 COPD patients during AECOPD were compared to convalescence values, 2 weeks after AECOPD, being higher during AECOPD [71]. Song et al., included 60 patients with AECOPD, of which 30 had acute respiratory failure type II and 30 did not have respiratory failure. COPD patients with respiratory failure type II demonstrated higher levels of D-dimer and fibrinogen. Moreover, in the group of COPD patients with respiratory failure type II, D-dimer and fibrinogen levels had significantly positive correlations with PaCO2 and negative correlations with PO2, highlighting the contribution of hypoxia and hypercapnia to prothrombotic tendency [72].

Van der Vorm et al., demonstrated that fibrinogen, FVIII, maximum amount of thrombin (nM/min), vWF Ag, and vWF Ac, were significantly elevated during AECOPD compared to convalescence values (8 weeks after AECOPD) [73]. Similarly, in the study by Elsalam et al., including patients with AECOPD and healthy control subjects, higher levels of soluble fibrin complex, D-dimers, TAT and fibrinogen were observed in COPD patients. In further analysis, patients with severe COPD illustrated higher levels of soluble fibrin complex, D-dimer, TAT, and fibrinogen, compared to patients with moderate disease. However, there was no statistically significant difference between COPD patients and control subjects regarding the level of AT, protein C, and protein S [74]. Daga et al., studied the levels of fibrinogen, vWF Ag, PT, and aPTT between patients with AECOPD and with stable disease. Fibrinogen and vWF Ag levels were higher during AECOPD, while no difference was observed for PT and aPTT [75]. In the study by Zhang et al., levels of D-dimer and fibrinogen were elevated in COPD patients compared to controls. Among the COPD patients, D-dimer and fibrinogen levels were further increased during exacerbation compared to the stable phase [12]. These 4 studies show that during AECOPD, D-dimer, TAT, vWF, and FVIII levels are amplified compared to stable COPD values.

Husebø et al., demonstrated that during AECOPD, all markers were higher than in the stable state; TAT, APC-PCI and D-dimer. Higher D-dimer in stable COPD predicted a higher mortality (HR: 1.60 (1.24–2.05), $p < 0.001$). Higher TAT was associated with both an increased risk of later exacerbations, with a yearly incidence rate ratio of 1.19 (1.04–1.37), and a faster time to the first exacerbation (HR: 1.25 (1.10–1.42)) ($p = 0.001$, for both after adjustment) [76]. In the study by Roland et al., examining TF levels in patients with COPD, during COPD exacerbation and 4–6 weeks later, TF levels were significantly higher during COPD exacerbation, while there was no correlation observed between the rise in TF, infection symptoms, and oxygen saturation during exacerbation; treatment with antibiotics or corticosteroids and TF levels during and after COPD exacerbation [77]. These 2 studies demonstrate that TAT, APC-PCI, D-dimer, and TF levels are increased during AECOPD compared to stable COPD.

Alterations of coagulation factors and inhibitors in patients with stable COPD and during COPD exacerbations are summarized in **Table 1**.

Author, Year	Participants	Disease Status	Results
Agale, 2018 [56]	50 patients with stable COPD vs. 50 healthy controls	Stable COPD	• Fibrinogen (mg/dL) (455.38 ± 159.71 vs. 255.50 ± 7.98)

Author, Year	Participants	Disease Status	Results
Arregui, 2010 [57]	51 patients with stable COPD vs. 30 healthy controls	Stable COPD	- Fibrinogen (mg/dL) (469.7 vs. 334.7) - D-dimers (μg/L) (339.3 vs. 244.7) - Factor VIII (%) (113.7 vs. 105.1) - vWF Ag (%) (113.8 vs. 110.9) - vWF Ac (%) (105.9 vs. 98.8)
Ashitani, 2002 [8]	40 patients with stable COPD vs. 20 healthy controls	Stable COPD	- TAT (ng/mL) (2.9 ± 1.6 vs. 1.8 ± 0.8) - FPA (ng/mL) (2.7 ± 0.9 vs. 1.2 ± 0.6) - tPA-PAI (ng/mL) (20.2 ± 9.3 vs. 13.8 ± 2.1) - β-thromboglobulin (ng/mL) (120.0 ± 61.1 vs. 46.3 ± 8.5)
Cella, 2001 [62]	14 patients with stable COPD vs. 20 healthy controls	Stable COPD	- Nitric oxide (μg/mL) (23.42 ± 1.67 vs. 40.0 ± 3.38) - Thrombomodulin (ng/mL) (5.46 ± 1.32 vs. 12.9 ± 0.51) - TFPI (ng/mL) (112.28 ± 6.45 vs. 77.68 ± 0.28)
Daga, 2020 [75]	30 patients with AECOPD vs. 30 stable COPD patients	AECOPD	Fibrinogen (mg/dL) (491.09 (406.86–575.31) vs. 426.86 (373.08–480.63))

Author, Year	Participants	Disease Status	Results
			• vWF Ag (147.58 (141.90–153.25) vs. 128.95 (117.07–140.83)) • PT (1.13 (1.09–1.18) vs. 1.09 (1.00–1.18)) [§] • aPTT (1.14 (1.06–1.22) vs. 1.14 (1.07–1.20)) [§]
Eickhoff, 2008 [54]	60 patients with stable COPD vs. 20 healthy controls	Stable COPD	• Fibrinogen (mg/dL) (426(354–472) vs. 382 (317–428))
Elsalam, 2013 [74]	38 patients with AECOPD vs. 25 healthy controls	AECOPD	• Soluble fibrin complex (μg/mL) (179.4 ± 73 vs. 3.1 ± 0.34) • D-dimers (ng/mL) (444 ± 225 vs. 371 ± 72.7) • TAT (ng/mL) (14.3 ± 4.0 vs. 3.6 ± 0.4) • Fibrinogen (mg/dL) (338.6 ± 45 vs. 151.6 ± 4.5)
	15 patients with severe COPD vs. 10 patients with moderate COPD	AECOPD	• Soluble fibrin complex (μg/mL) (231.3 ± 5 vs. 101.7 ± 34) • D-dimers (ng/mL) (307.2 ± 85.9 vs. 198 ± 70) • TAT (ng/mL) (17.3 ± 2.6 vs. 9.2 ± 1) • Fibrinogen (mg/dL) (361.5 ± 41 vs. 297.7 ± 37)

Author, Year	Participants	Disease Status	Results
Garcia-Rio, 2010 [53]	324 patients with stable COPD vs. 110 healthy controls	Stable COPD	• Fibrinogen (mg/dL) (370 (310–410) vs. 300 (250–350))
Husebø, 2021 [76]	413 patients with stable COPD vs. 49 healthy controls	Stable COPD	• TAT (ng/mL) (1.03 (0.76–1.44)) vs. (1.28 (1.04–1.49))
	148 COPD patients during AECOPD and compared to baseline values	AECOPD	• TAT (ng/mL) (2.56 (1.74–3.95) vs. 1.43 (0.97–1.88)) • APC-PCI (ng/mL) (489.3 (340.5–770.3) vs. 416.4 (295.5–564.3)) • D-dimers (ng/mL) (763.5 (491–1192) vs. 479.7 (273–742))
Jankowski, 2011 [11]	60 stable COPD patients	Stable COPD	• FXIa was detected in 9 (15%) and TF activity in 7 (11.7%) patients. • Those patients had higher: ✓ prothrombin fragment 1 + 2 (398 (216) vs. 192 (42)) ✓ fibrinogen (g/L) (5.58 (2.01) vs. 3.97 (2.47))
Koutsokera, 2009 [68]	30 COPD patients during AECOPD and compared to convalescence values (40 days after AECOPD)	AECOPD	• Fibrinogen (mg/dL) (545.1 ± 35.9 vs. 455.4 ± 30.0)
Kyriakopoulos, 2020 [59]	103 patients with stable COPD vs. 42 COPD-free smokers	Stable COPD	• D-dimers (ng/mL) (540 ± 940 vs. 290 ± 140)

Author, Year	Participants	Disease Status	Results
			• Fibrinogen (mg/dL) (399 ± 82 vs. 346 ± 65) • FII (%) (122 ± 22 vs. 109 ± 19) • FV (%) (131 ± 25 vs. 121 ± 19) • FVIII (%) (143 ± 32 vs. 122 ± 20) • FX (%) (114 ± 23 vs. 100 ± 16) • Protein S (%) (95.1 ± 18.74 vs. 110.5 ± 17.9) • AT (%) (94.4 ± 11.5 vs. 102.3 ± 13.2)
Maclay, 2011 [71]	18 patients with stable COPD vs. 16 healthy controls	Stable COPD	• Fibrinogen (g/L) (2.8 (0.5) vs. 2.7 (0.5)) • Platelet-monocyte aggregates (%) (25.3 (8.3) vs. 19.5 (4.0)) • D-dimers (ng/mL) (373 (137) vs. 341 (202)) [§]
	12 COPD patients during AECOPD and compared to convalescence values (2 weeks after AECOPD)	AECOPD	• Platelet-monocyte aggregates (%) (32.0 (11.0) vs. 25.5 (6.4))
Polatli, 2008 [58]	33 patients with stable COPD vs. 16 healthy controls	Stable COPD	• Fibrinogen (mg/dL) (346.88 ± 92.3 vs. 289.99 ± 39.9) • vWF (%) (178.26 ± 118.3 vs. 142.85 ± 57.16) [§] • MAB (20.98 ± 28.74 vs. 10.47 ± 8.08) [§]

Author, Year	Participants	Disease Status	Results
	26 patients during AECOPD vs. 33 stable COPD patients	AECOPD	• Fibrinogen (mg/dL) (447.67 ± 128 vs. 346.88 ± 92.3) • vWF (%) (257.39 ± 157 vs. 178.26 ± 118.3) • MAB (34.99 ± 46.35 vs. 20.98 ± 28.74) §
Roland, 1999 [77]	30 COPD patients during AECOPD and compared to baseline values (4–6 weeks later)	AECOPD	• TF (65.09 (0.00–153.80) vs. 5.92 (0.00–121.30))
Saldias, 2012 [67]	85 COPD patients during AECOPD and compared to baseline values	AECOPD	• Fibrinogen (mg/dL) (395.2 ± 104.1 vs. 319.9 ± 57.1)
Samareh, 2000 [55]	31 patients with stable COPD vs. 29 healthy controls	Stable COPD	• Fibrinogen (g/L) (3.81 ± 0.93 vs. 3.72 ± 0.9) §
Silva, 2012 [78]	58 patients with stable COPD vs. 30 healthy controls	Stable COPD	• D-dimers (ng/mL) (0.24 (0.2–0.36) vs. 0.17 (0.12–0.24)) §
Song, 2013 [72]	30 AECOPD patients with ARF II vs. 30 AECOPD patients without ARF II	AECOPD	• D-dimers(mg/L) (0.36 ± 0.26 vs. 0.11 ± 0.08) • Fibrinogen (g/L) (4.40 ± 0.64 vs. 3.20 ± 0.64)
Szczypiorska, 2015 [61]	66 patients with stable COPD vs. 25 healthy controls	Stable COPD	• TF (118.3 (27.2–373.2) vs. 83.1 (18.3–264.1)) • TFPI (120.2 (52.2–323.6) vs. 96.1 (41.2–150.2))

Author, Year	Participants	Disease Status	Results
			• Fibrinogen (mg/dL) (423 (323–523) vs. 359 (259–459)) • aPTT (36.0 (33–39) vs. 39.8 (35–45))
Thomas, 2016 [70]	20 patients with stable COPD vs. 20 healthy controls	Stable COPD	• Fibrinogen (mg/dL) (226.2 vs. 162.7)
	20 patients during AECOPD vs. 20 stable COPD patients	AECOPD	• Fibrinogen (mg/dL) (275.55 vs. 226.2)
Undas, 2011 [14]	60 patients with stable COPD vs. 43 non-COPD smokers	Stable COPD	• Fibrinogen (mg/dL) (414 ± 160 vs. 285 ± 55) • FII (%) (115 ± 16 vs. 102 ± 10) • FV (%) (114 ± 19 vs. 102 ± 12) • FVII (%) (111 ± 15 vs. 102 ± 17) • FVIII (%) (170 ± 34 vs. 115 ± 27) • FIX (119 ± 21 vs. 107 ± 17) • FX (%) (117 ± 21 vs. 110 ± 19) § • Free TFPI (ng/mL) (17.7 ± 3.2 vs. 18.9 ± 3.2) • Maximum thrombin levels (404 ± 76 vs. 317 ± 62)

Author, Year	Participants	Disease Status	Results
			• Total thrombin (92.7 ± 23.0 vs. 81.0 ± 16.5)
Vaidyula, 2009 [60]	11 patients with stable COPD vs. 10 healthy controls	Stable COPD	• TF procoagulant activity (52.3 ± 5.6 vs. 20.7 ± 1.5) • TAT (ng/mL) (2.99 ± 0.65 vs. 1.31 ± 0.13)
Valipour, 2008 [69]	30 patients with stable COPD vs. 30 healthy controls	Stable COPD	• Fibrinogen (mg/dL) (424 (358–459) vs. 360 (326–393))
	30 COPD patients during AECOPD and compared to convalescence values (6 weeks after AECOPD)	AECOPD	• Fibrinogen (mg/dL) (419 (329–470) vs. 311 (249–401))
	30 patients during AECOPD vs. 30 healthy controls	AECOPD	• Fibrinogen (mg/dL) (419 (329–470) vs. 360 (326–393))
Van der Vorm, 2020 [73]	52 COPD patients during AECOPD and compared to convalescence values * (8 weeks after AECOPD)	AECOPD	• Fibrinogen (g/L) (4.8 ± 1.5 vs. 4.2 ± 1.3) • FVIII (%) (185 (91) vs. 153 (84)) • Maximum amount of thrombin (nM/min) (1503 ± 335 vs. 1400 ± 360) • vWF Ag (%) (218 (113) vs. 182 (110)) • vWF Ac (%) (157 (89) vs. 135 (71))
Waschki, 2017 [63]	74 patients with stable COPD vs. 18 healthy controls	Stable COPD	• Plasminogen activator inhibitor (ng/mL) (13 (10–17) vs. 11 (8–13))

Author, Year	Participants	Disease Status	Results
Wedzicha, 2000 [34]	67 COPD patients during AECOPD and compared to baseline values	AECOPD	• Fibrinogen (g/L) (4.26 ± 1.41 vs. 3.9 ± 0.67)
Zhang, 2016 [12]	43 patients with stable COPD vs. 43 healthy controls	Stable COPD	• D-dimers (µg/L) (1799 (1205–2196) vs. 433 (369–456)) • Fibrinogen (mg/dL) (297 ± 34.3 vs. 271 ± 66.8)
	43 COPD patients during AECOPD and compared to baseline values	AECOPD	• D-dimers (µg/L) (2839 (2078–4389) vs. 1799 (1205–2196)) • Fibrinogen (mg/dL) (352 ± 81.3 vs. 297 ± 34.3)

Values are presented as mean ± SD or median (IQR). § Without statistical significance. * Convalescence values available for 32 patients.

5. Conclusions

To the best of our knowledge, this is the first comprehensive review of studies on hypercoagulability either in stable COPD or during COPD exacerbations. A large body of epidemiological data supports the hypothesis that COPD is closely linked to a hypercoagulable state. Overall, patients with stable COPD exhibit major alterations of fibrinogen, FII, FV, FVII, FVIII, FIX, D-dimers, von Willebrand factor Ag, von Willebrand factor Ac, TF, TAT, FPA, β-thromboglobulin, tPA-PAI, prothrombin fragment 1 and 2, and maximum thrombin levels, pointing to hypercoagulability. Prothrombotic state is further enhanced during exacerbations, reflected by a significant increase of TF, TAT, soluble fibrin complex, fibrinogen, D-dimers, and APC-PCI. This summary provides an in-depth overview on the alterations of coagulation factors and prothrombotic changes in COPD patients that enhance our understanding of the coexistence of cardiovascular comorbidities in these patients.

References

1. Adeloye, D.; Chua, S.; Lee, C.; Basquill, C.; Papana, A.; Theodoratou, E.; Nair, H.; Gasevic, D.; Sridhar, D.; Campbell, H.; et al. Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. J. Glob. Health 2015, 5, 020415.

2. The Top 10 Causes of Death. Available online: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death (accessed on 28 May 2021).

3. Schneider, C.; Bothner, U.; Jick, S.S.; Meier, C.R. Chronic obstructive pulmonary disease and the risk of cardiovascular diseases. Eur. J. Epidemiol. 2010, 25, 253–260.

4. Chen, W.; Thomas, J.; Sadatsafavi, M.; FitzGerald, J.M. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. Lancet Respir. Med. 2015, 3, 631–639.

5. Lankeit, M.; Held, M. Incidence of venous thromboembolism in COPD: Linking inflammation and thrombosis? Eur. Respir. J. 2016, 47, 369–373.

6. Sin, D.D.; Wu, L.; Paul Man, S.F. The relationship between reduced lung function and cardiovascular mortality. Chest 2005, 127, 1952–1959.

7. Abduganieva, E.; Artikov, D.; Liverko, I. Hypercoagulation as the main cause of death in COPD. In Proceedings of the ERS International Congress 2019 Abstracts, Madrid, Spain, 28 September–2 October 2019.

8. Ashitani, J.-I.; Mukae, H.; Arimura, Y.; Matsukura, S. Elevated plasma procoagulant and fibrinolytic markers in patients with chronic obstructive pulmonary disease. Intern. Med. 2002, 41, 181–185.

9. Wanner, A.; Schmid, A. Faculty opinions recommendation of fibrin clot properties are altered in patients with chronic obstructive pulmonary disease. Beneficial effects of simvastatin treatment. Natl. Libr. Med. 2010, 102, 1176–1182.

10. Sambola, A.; Osende, J.; Hathcock, J.; Degen, M.; Nemerson, Y.; Fuster, V.; Crandall, J.; Badimon, J.J. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. Circulation 2003, 107, 973–977.

11. Jankowski, M.; Undas, A.; Kaczmarek, P.; Butenas, S. Activated factor XI and tissue factor in chronic obstructive pulmonary disease: Links with inflammation and thrombin generation. Thromb. Res. 2011, 127, 242–246.

12. Zhang, M.; Zhang, J.; Zhang, Q.; Yang, X.; Shan, H.; Ming, Z.; Chen, H.; Liu, Y.; Yin, J.; Li, Y. D-Dimer as a potential biomarker for the progression of COPD. Clin. Chim. Acta 2016, 455, 55–59.

13. Zuur-Telgen, M.; van der Valk, P.; Zuur, B.; van der Palen, J.; Kerstjens, H.; Brusse-Keizer, M. Stable state fibrinogen is additive to Mr-proADM as a predictor of mortality in COPD patients. Eur. Res. J. 2015, 46, 3362.

14. Undas, A.; Jankowski, M.; Kaczmarek, P.; Sladek, K.; Brummel-Ziedins, K. Thrombin generation in chronic obstructive pulmonary disease: Dependence on plasma factor composition. Thromb. Res. 2011, 128, e24–e28.

15. Mispelaere, D.; Glerant, J.C.; Audebert, M.; Remond, A.; Sevestre-Pietri, M.A.; Jounieaux, V. Pulmonary embolism and sibilant types of chronic obstructive pulmonary disease decompensations. Rev. Mal. Respir. 2002, 19, 415–423.

16. Kim, V.; Goel, N.; Gangar, J.; Zhao, H.; Ciccolella, D.; Silverman, E.; Crapo, J.; Criner, G. Risk Factors for venous thromboembolism in chronic obstructive pulmonary disease. Chronic Obstr. Pulm. Dis. 2014, 1, 239–249.

17. Gan, W.Q. Association between chronic obstructive pulmonary disease and systemic inflammation: A systematic review and a meta-analysis. Thorax 2004, 59, 574–580.

18. Koupenova, M.; Kehrel, B.E.; Corkrey, H.A.; Freedman, J.E. Thrombosis and platelets: An update. Eur. Heart J. 2017, 38, 785–791.

19. Wang, Q.; Zennadi, R. Oxidative stress and thrombosis during aging: The roles of oxidative stress in RBCs in venous thrombosis. Int. J. Mol. Sci. 2020, 21, 4259.

20. Bärtsch, P. How thrombogenic is hypoxia? JAMA 2006, 295, 2297–2299.

21. Sabit, R.; Thomas, P.; Shale, D.J.; Collins, P.; Linnane, S.J. The effects of hypoxia on markers of coagulation and systemic inflammation in patients with COPD. Chest 2010, 138, 47–51.

22. Lonergan, M.; Dicker, A.J.; Crichton, M.L.; Keir, H.R.; van Dyke, M.K.; Mullerova, H.; Miller, B.E.; Tal-Singer, R.; Chalmers, J.D. Blood neutrophil counts are associated with exacerbation frequency and mortality in COPD. Respir. Res. 2020, 21, 166.

23. Iba, T.; Levy, J.H. Inflammation and thrombosis: Roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J. Thromb. Haemost. 2018, 16, 13911.

24. Sin, D.D.; Man, S.F. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? the potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 2003, 107, 1514–1519.

25. Van der Meijden, P.E.J.; Heemskerk, J.W.M. Platelet biology and functions: New concepts and clinical perspectives. Nat. Rev. Cardiol. 2019, 16, 166–179.

26. Gutmann, C.; Siow, R.; Gwozdz, A.M.; Saha, P.; Smith, A. Reactive oxygen species in venous thrombosis. Int. J. Mol. Sci. 2020, 21, 1918.

27. Darbousset, R.; Thomas, G.M.; Mezouar, S.; Frère, C.; Bonier, R.; Mackman, N.; Renné, T.; Dignat-George, F.; Dubois, C.; Panicot-Dubois, L. Tissue factor–positive neutrophils bind to injured endothelial wall and Initiate thrombus formation. Blood 2012, 120, 2133–2143.

28. Gupta, N.; Zhao, Y.-Y.; Evans, C.E. The stimulation of thrombosis by hypoxia. Thromb. Res. 2019, 181, 77–83.

29. Mackman, N. Role of tissue factor in hemostasis, thrombosis, and vascular development. Arter. Thromb. Vasc. Biol. 2004, 24, 1015–1022.

30. Prchal, J.T. Hypoxia and thrombosis. Blood 2018, 132, 348–349.

31. Couturaud, F.; Bertoletti, L.; Pastre, J.; Roy, P.-M.; Le Mao, R.; Gagnadoux, F.; Paleiron, N.; Schmidt, J.; Sanchez, O.; De Magalhaes, E.; et al. Prevalence of pulmonary embolism among patients with COPD hospitalized with acutely worsening respiratory symptoms. JAMA 2021, 325, 59–68.

32. Aleva, F.E.; Voets, L.W.L.M.; Simons, S.O.; de Mast, Q.; van der Ven, A.J.A.M.; Heijdra, Y.F. Prevalence and localization of pulmonary embolism in unexplained acute exacerbations of COPD: A systematic review and meta-analysis. Chest 2017, 151, 544–554.

33. Polosa, R.; Malerba, M.; Cacciola, R.R.; Morjaria, J.B.; Maugeri, C.; Prosperini, G.; Gullo, R.; Spicuzza, L.; Radaeli, A.; Di Maria, G.U. Effect of acute exacerbations on circulating endothelial, clotting and fibrinolytic markers in COPD patients. Intern. Emerg. Med. 2013, 8, 567–574.

34. Wedzicha, J.A.; Seemungal, T.A.; MacCallum, P.K.; Paul, E.A.; Donaldson, G.C.; Bhowmik, A.; Jeffries, D.J.; Meade, T.W. Acute exacerbations of chronic obstructive pulmonary disease are accompanied by elevations of plasma fibrinogen and serum IL-6 levels. Thromb. Haemost. 2000, 84, 210–215.

35. Smeeth, L.; Cook, C.; Thomas, S.; Hall, A.J.; Hubbard, R.; Vallance, P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006, 367, 1075–1079.

36. Schmidt, M.; Horvath-Puho, E.; Thomsen, R.W.; Smeeth, L.; Sørensen, H.T. Acute infections and venous thromboembolism. J. Intern. Med. 2012, 271, 608–618.

37. Pottier, P.; Hardouin, J.B.; Lejeune, S.; Jolliet, P.; Gillet, B.; Planchon, B. Immobilization and the risk of venous thromboembolism. A meta-analysis on epidemiological studies. Thromb. Res. 2009, 124, 468–476.

38. Dentali, F.; Pomero, F.; Micco, P.D.; La Regina, M.; Landini, F.; Mumoli, N.; Pieralli, F.; Giorgi-Pierfranceschi, M.; Re, R.; Vitale, J.; et al. Prevalence and risk factors for pulmonary embolism in patients with suspected acute exacerbation of COPD: A multi-center study. Eur. J. Intern. Med. 2020, 80, 54–59.

39. Weitzenblum, E.; Chaouat, A.; Kessler, R.; Canuet, M. Overlap syndrome: Obstructive sleep apnea in patients with chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. 2008, 5, 237–241.

40. Colten, H.R.; Altevogt, B.M. Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem; National Academies Press: Washington, DC, USA, 2006.

41. Fernández-Bello, I.; Monzón, M.E.; García Río, F.; Justo, S.R.; Cubillos-Zapata, C.; Casitas, R.; Sánchez, B.; Jaureguizar, A.; Acuña, P.; Alonso-Fernández, A.; et al. Procoagulant state of sleep apnea depends on systemic inflammation and endothelial damage. Arch. Bronconeumol. 2020, 20, 30546–30549.

42. Xu, J.; Wang, X.; Meng, F.; Zhao, T.; Tang, T.; Wu, W.; Wang, W. The role of obstructive sleep apnea on the prognosis of pulmonary embolism: A systemic review and meta-analysis. Sleep Breath. 2020, 24, 1–8.

43. Xie, J.; Li, F.; Wu, X.; Hou, W. Prevalence of pulmonary embolism in patients with obstructive sleep apnea and chronic obstructive pulmonary disease: The overlap syndrome. Heart Lung 2019, 48, 261–265.

44. Loeffen, R.; Spronk, H.M.H.; Ten Cate, H. The impact of blood coagulability on atherosclerosis and cardiovascular disease. J. Thromb. Haemost. 2012, 10, 1207–1216.

45. Borissoff, J.I.; Spronk, H.M.H.; ten Cate, H. The hemostatic system as a modulator of atherosclerosis. N. Engl. J. Med. 2011, 364, 1746–1760.

46. Ye, Z.; Liu, E.H.C.; Higgins, J.P.T.; Keavney, B.D.; Lowe, G.D.O.; Collins, R.; Danesh, J. Seven haemostatic gene polymorphisms in coronary disease: Meta-Analysis of 66,155 CASES and 91,307 controls. Lancet 2006, 367, 651–658.

47. Elsevier Guyton and Hall Textbook of Medical Physiology. Available online: https://www.elsevier.com/books/guyton-and-hall-textbook-of-medical-physiology/hall/978-1-4557-7005-2 (accessed on 11 May 2021).

48. Marder, V.J.; Aird, W.C.; Bennett, J.S.; Schulman, S.; White, G.C., II. Hemostasis and Thrombosis: Basic Principles and Clinical Practice; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2012; ISBN 9781451177695.

49. Tapson, V.F. The role of smoking in coagulation and thromboembolism in chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. 2005, 2, 71–77.

50. Goldhaber, S.Z.; Tapson, V.F. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. Am. J. Cardiol. 2004, 93, 259–262.

51. Bertoletti, L.; Quenet, S.; Laporte, S.; Sahuquillo, J.C.; Conget, F.; Pedrajas, J.M.; Martin, M.; Casado, I.; Riera-Mestre, A.; Monreal, M. Pulmonary embolism and 3-month outcomes in 4036 patients with venous thromboembolism and chronic obstructive pulmonary disease: Data from the RIETE registry. Respir. Res. 2013, 14, 75.

52. Mannino, D.M.; Ford, E.S.; Redd, S.C. Obstructive and restrictive lung disease and markers of inflammation: Data from the third national health and nutrition examination. Am. J. Med. 2003, 114, 758–762.

53. Garcia-Rio, F.; Miravitlles, M.; Soriano, J.B.; Muñoz, L.; Duran-Tauleria, E.; Sánchez, G.; Sobradillo, V.; Ancochea, J. EPI-SCAN steering committee systemic inflammation in chronic obstructive pulmonary disease: A population-based study. Respir. Res. 2010, 11, 63.

54. Eickhoff, P.; Valipour, A.; Kiss, D.; Schreder, M.; Cekici, L.; Geyer, K.; Kohansal, R.; Burghuber, O.C. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 2008, 178, 777–780.

55. Samareh, M.F.; Khorasani, S.B.R.; Shadkam, S. Correlation of CRP and serum fibrinogen levels with disease severity, clinical factors and pulmonary function tests in COPD patients. Tanaffos 2010, 9, 28–33.

56. Agale, S.A. Serum fibrinogen level in COPD patients—A comparative study. J. Med. Sci. Clin. Res. 2018, 6, 701–703.

57. Arregui, M.A.; Ezquerra, K.L.; López, F.C.; Lacasa, R.C. Hypercoagulability state and endotelial injury in stable chronic obstructive pulmonary disease patients. An. Sist. Sanit. Navar. 2010, 33, 43–50.

58. Polatli, M.; Cakir, A.; Cildag, O.; Bolaman, A.Z.; Yenisey, C.; Yenicerioglu, Y. Microalbuminuria, von willebrand factor and fibrinogen levels as markers of the severity in COPD exacerbation. J. Thromb. Thrombolysis 2008, 26, 97–102.

59. Kyriakopoulos, C.; Chronis, C.; Tatsioni, A.; Papapetrou, E.; Gogali, A.; Vaggeli, K.; Katsanos, C.; Tsaousi, C.; Tsalepi, C.; Charisis, A.; et al. Hypercoagulability in patients with stable COPD assessed by coagulation factor levels. Eur. Respir. J. 2020, 56 (Suppl. 64), 3578.

60. Vaidyula, V.R.; Criner, G.J.; Grabianowski, C.; Rao, A.K. Circulating tissue factor procoagulant activity is elevated in stable moderate to severe chronic obstructive pulmonary disease. Thromb. Res. 2009, 124, 259–261.

61. Szczypiorska, A.; Czajkowska-Malinowska, M.; Góralczyk, B.; Bielis, L.; Drela, E.; Góralczyk, K.; Ruszkowska-Ciastek, B.; Rość, D. Tissue factor and tissue factor pathway Inhibitor in chronic obstructive pulmonary disease. Med. Res. J. 2015, 3, 32–37.

62. Cella, G.; Sbarai, A.; Mazzaro, G.; Vanzo, B.; Romano, S.; Hoppensteadt, T.; Fareed, J. Plasma markers of endothelial dysfunction in chronic obstructive pulmonary disease. Clin. Appl. Thromb. Hemost. 2001, 7, 205–208.

63. Waschki, B.; Watz, H.; Holz, O.; Magnussen, H.; Olejnicka, B.; Welte, T.; Rabe, K.F.; Janciauskiene, S. Plasminogen activator inhibitor-1 is elevated in patients with COPD

independent of metabolic and cardiovascular function. Int. J. Chron. Obstr. Pulm. Dis. 2017, 12, 981–987.

64. Pang, H.; Wang, L.; Liu, J.; Wang, S.; Yang, Y.; Yang, T.; Wang, C. The prevalence and risk factors of venous thromboembolism in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease. Clin. Respir. J. 2018, 12, 2573–2580.

65. Zielinski, J.; MacNee, W.; Wedzicha, J.; Ambrosino, N.; Braghiroli, A.; Dolensky, J.; Howard, P.; Gorzelak, K.; Lahdensuo, A.; Strom, K.; et al. Causes of death in patients with COPD and chronic respiratory failure. Monaldi Arch. Chest Dis. 1997, 52, 43–47.

66. Kim, T.H.; Oh, D.K.; Oh, Y.-M.; Lee, S.W.; Do Lee, S.; Lee, J.S. Fibrinogen as a potential biomarker for clinical phenotype in patients with chronic obstructive pulmonary disease. J. Thorac. Dis. 2018, 10, 5260–5268.

67. Saldías, P.F.; Díaz, P.O.; Dreyse, D.J.; Gaggero, B.A.; Sandoval, A.C.; Lisboa, B.C. Etiology and Biomarkers of Systemic Inflammation in Mild to Moderate COPD Exacerbations. Rev. Med. Chil. 2012, 140, 10.

68. Koutsokera, A.; Kiropoulos, T.S.; Nikoulis, D.J.; Daniil, Z.D.; Tsolaki, V.; Tanou, K.; Papaioannou, A.I.; Germenis, A.; Gourgoulianis, K.I.; Kostikas, K. Clinical, functional and biochemical changes during recovery from COPD exacerbations. Respir. Med. 2009, 103, 919–926.

69. Valipour, A.; Schreder, M.; Wolzt, M.; Saliba, S.; Kapiotis, S.; Eickhoff, P.; Burghuber, O.C. Circulating vascular endothelial growth factor and systemic inflammatory markers in patients with stable and exacerbated chronic obstructive pulmonary disease. Clin. Sci. 2008, 115, 225–232.

70. Thomas, B.; Yuvarajan, S. Plasma fibrinogen in chronic obstructive pulmonary disease—A cross sectional study conducted in a tertiary care hospital in puducherry, India. Br. J. Med. Med. Res. 2016, 14, 1–8.

71. Maclay, J.D.; McAllister, D.A.; Johnston, S.; Raftis, J.; McGuinnes, C.; Deans, A.; Newby, D.E.; Mills, N.L.; MacNee, W. Increased platelet activation in patients with stable and acute exacerbation of COPD. Thorax 2011, 66, 769–774.

72. Song, Y.-J.; Zhou, Z.-H.; Liu, Y.-K.; Rao, S.-M.; Huang, Y.-J. Prothrombotic state in senile patients with acute exacerbations of chronic obstructive pulmonary disease combined with respiratory failure. Exp. Ther. Med. 2013, 5, 1184–1188.

73. Van der Vorm, L.N.; Li, L.; Huskens, D.; Hulstein, J.J.J.; Roest, M.; de Groot, P.G.; Ten Cate, H.; de Laat, B.; Remijn, J.A.; Simons, S.O. Acute exacerbations of COPD are associated with a prothrombotic state through platelet-monocyte complexes, endothelial activation and increased thrombin generation. Respir. Med. 2020, 171, 106094.

74. Elsalam, H.M.A.; Mohamed, M.A.; El Gammal, M.S.; El-Shabrawy, M. Hypercoagulability in different respiratory diseases. Egypt. J. Chest Dis. Tuberc. 2013, 62, 331–341.

75. Daga, M.K.; Kumar, N.; Mawari, G.; Singh, S.; Mahapatra, S.J.; Hussain, M.; Jha, M.K. Study of prothrombotic markers in COPD. J. Adv. Res. Med. 2020, 7, 1–6.

76. Husebø, G.R.; Gabazza, E.C.; D'Alessandro Gabazza, C.; Yasuma, T.; Toda, M.; Aanerud, M.; Nielsen, R.; Bakke, P.S.; Eagan, T.M.L. Coagulation markers as predictors for clinical events in COPD. Respirology 2021, 26, 342–351.

77. Roland, M.A.; Seemungal, T.A.R.; Bhowmik, A.; Sapsford, R.J.; Wedzicha, J.A.; MacCallum, P.K. P17 Effect of exacerbation on plasma levels of tissue factor in patients with COPD. Blood Coagul. Fibrinolysis 1999, 10, 544.

78. Silva, D.R.; Coelho, A.C.; Gazzana, M.B.; Menna Barreto, S.S.; Knorst, M.M. D-Dimer levels in stable COPD patients: A case-control study. Chronic Obstr. Pulm. Dis. 2012, 9, 426–431.

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