

## **Chronic Obstructive Pulmonary Disease and Risk of Mortality in Patients with Venous Thromboembolism - The Tromsø Study**

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Short title: COPD and risk of mortality after VTE

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<b>What is known on this topic</b>	<b>What this paper adds</b>
<ul style="list-style-type: none"><li>• COPD is associated with venous thromboembolism (VTE) and mortality.</li><li>• COPD is associated with an inactive lifestyle, and physical inactivity is associated with increased mortality</li></ul>	<ul style="list-style-type: none"><li>• In VTE patients, severe COPD is associated with an increased risk of death</li><li>• The increased risk of death in VTE patients with severe COPD was not explained by physical inactivity.</li></ul>

## **Abstract**

**Background:** Previous studies have shown increased mortality in venous thromboembolism (VTE) patients with chronic obstructive pulmonary disease (COPD), but it is unknown to what extent the association is influenced by the severity of COPD and physical inactivity.

**Objectives:** To investigate whether COPD, and stages of COPD, influenced the risk of mortality after a first episode of VTE when physical inactivity was taken into account.

**Methods:** Patients with a first lifetime VTE (n=256) were recruited among individuals who participated and performed spirometry in the fifth (2001-02) and sixth (2007-08) surveys of the Tromsø Study (n=9577). All-cause mortality was registered up to December 31, 2015.

**Results:** There were 123 deaths during a median of 2.9 years of follow-up. The overall mortality rate was 11.9 (95% CI 10.0-14.2) per 100 person-years. The risk of death was 2-fold higher in COPD patients compared to those with normal airflow (HR 2.00, 95% CI 1.30-3.08) after multivariable adjustment. The risk of death increased with the severity of COPD. VTE patients with COPD stage III/IV had a 5-fold increased risk of death (HR 5.20, 95% CI 2.65-10.2) compared to those without COPD, and 50% of these patients died within 3.5 months after the incident VTE event. Adjustment for physical inactivity had minor effect on the risk estimates.

**Conclusions:** VTE patients with COPD had increased risk of death, particularly patients with severe COPD. The detrimental effect of COPD on mortality in VTE patients was apparently explained by factors other than physical inactivity among patients with COPD.

## Introduction

Venous thromboembolism (VTE), a collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common disease with serious short- and long-term complications (1-3). The 30-day case-fatality rate after a first VTE is reported to be 5-10% (4-6), and the overall 1-year mortality rate is around 20-25% (4-6). In patients with PE, the most common cause of early mortality is related to the PE itself (7). In the absence of recurrent VTE, long-term mortality is often attributed to comorbid conditions rather than to the VTE itself (8). Identification of subjects with high mortality risk is of importance for risk stratification and management of VTE patients.

Chronic obstructive pulmonary disease (COPD) is a public health concern due to frequent hospitalizations, severe co-morbidities, and a high mortality rate (9, 10). Among patients hospitalized for acute COPD-exacerbation, 5-10% die during hospitalization and 20% die during the first year after hospital discharge (11, 12). Results from registry-based studies and cohorts have shown that COPD is associated with a 2- to 5-fold increased risk of VTE (13-16), and the prevalence of acute PE is high (15-30%) in COPD patients hospitalized with suspected acute exacerbation (13, 17, 18). A concomitant VTE is associated with prolonged hospital stay and higher 1-year mortality in COPD patients (19).

Few studies have investigated the impact of concurrent respiratory disease on mortality risk in patients with VTE. A 1.4 to 2.2-fold higher risk of mortality has been reported in VTE patients (20, 21) and PE patients (22) with concurrent COPD compared to those without COPD. However, in these studies, information on the COPD diagnosis was abstracted from the medical records (20-23) without differentiating between stages of COPD. In addition, these studies did not take into account that COPD, and particularly severe COPD, is associated with an inactive lifestyle (24, 25) which has a detrimental influence on mortality risk (21, 26, 27). Consequently, it was not possible to draw conclusions about the risk of death according to the severity of COPD in VTE patients, and to determine to what extent the increased mortality in COPD patients with VTE was explained by

physical inactivity. Therefore, we aimed to investigate whether severity of COPD influenced mortality after a first episode of VTE when physical inactivity was taken into account.

## **Methods**

### **Study population**

Patients with a first lifetime VTE (n=256) were recruited among participants in the fifth (2001-02) and sixth (2007-08) surveys of the Tromsø Study (28), a cohort of individuals derived from the general population of Tromsø municipality in Norway, during the period 2001-2015 (n=9577). The medical record for each potential case of VTE was reviewed by trained personnel, and a VTE was considered verified when presence of clinical signs and symptoms of DVT or PE were combined with objective confirmation tests (compression ultrasonography, venography, spiral computed tomography, perfusion-ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment, as previously described in detail (29). VTE cases derived from the autopsy registry were recorded when the death certificate indicated VTE as cause of death or as a significant condition associated with death. The study was approved by the regional committee for health and research ethics, and all participants gave their informed written consent.

### **Assessment and classification of chronic obstructive pulmonary disease (COPD)**

Spirometry was assessed at enrolment in the Tromsø study, as previously described in detail (16). The American Lung Association criteria for spirometry testing were followed (30). Current drug therapy was not interrupted before the test. Reversibility test was not performed. Predicted values of forced expiratory volume in 1 second (FEV<sub>1</sub>), forced vital capacity (FVC) and FEV<sub>1</sub>/FVC ratio were calculated according to Langhammer et al. (31). Spirometry was accepted in subjects who expired for more than 3 seconds. To avoid misclassification of healthy subjects as obstructive, those with FEV<sub>1</sub>/FVC <0.7 or predicted FEV<sub>1</sub> <80% were excluded from the analyses if peak expiratory flow (PEF) was below 3 x forced expiratory flow when 75% of the air had been expired (PEF >3 x FEF<sub>75</sub>) (32).

The subjects were allocated into four groups based on lung function according to the Global Initiative of Chronic Obstructive Lung Disease (GOLD) guidelines (33). Due to few subjects with severe obstruction, participants with COPD stages III and IV (predicted FEV1 <50% combined with a FEV1/FVC ratio <0.7) were merged into one category for the analyses.

### **Other measurements**

Height and weight were measured at enrolment in the Tromsø study with subjects wearing light clothes and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m<sup>2</sup>). Information on smoking status (current, former, never), physical activity, dyspnea (when walking calmly, washing/dressing or at rest), daily cough and history of cardiovascular disease (myocardial infarction, stroke or angina pectoris) was collected from a self-administered questionnaire. We classified subjects as inactive (i.e. 'no activity' or '< 1 h per week) or active (i.e. '≥ 1 h per week') based on their reported weekly amount of light and hard physical activity, as previously described in detail (34). Information on active cancer at the time of the VTE, and acute medical conditions (including myocardial infarction, stroke, and acute infections) in the three months preceding the VTE, was extracted by thorough review of medical records using a standardized form.

### **Outcomes**

Death from any cause was the primary outcome, and information on all-cause mortality was obtained from the National Population Registry of Norway.

### **Statistical analyses**

For each individual, person-time of follow up was accrued from the date of the first VTE to the date of death or study end (December 31, 2015). Mortality rates (MR) were calculated and expressed as number of deaths per 100 person-years. A Kaplan Meier plot was made to display the ten-year

survival after VTE according to stages of COPD. Cox-regression models were used to estimate hazard ratios (HR) with 95% confidence interval (CI) for all-cause mortality according to stages of COPD. Analyses were conducted for overall VTE and in subgroups according to clinical presentation (i.e. PE and DVT). In order to adjust for age and sex, age was used as time-scale and sex was included as a co-variate in the regression model. In a second adjustment model, physical activity was added, and in a third adjustment model, we adjusted for age (time scale), sex, physical activity, BMI, smoking status, active cancer, history of cardiovascular diseases, and acute medical conditions. The proportional hazards assumption was tested using Schoenfeld residuals, and was not violated.

## Results

Among the 256 subjects with VTE, 161 (62.9%) had normal airflow, 35 (13.7%) had COPD stage I, 44 (17.1%) had COPD stage II and 16 (6.3%) had COPD stages III/IV (Table 1). Patients with COPD stage III/IV were older (mean age 76.3 versus 73.1 years) and had lower BMI (25.8 versus 28.7 kg/m<sup>2</sup>) compared with those with normal airflow. Moreover, the proportions of current smokers (56.3% versus 12.5%) and patients with active cancer (43.8% versus 31.1%) were higher among those with COPD stage III/IV.

The median follow-up time after VTE was 2.9 years (range 1 day to 13.9 years). During follow-up, 123 patients died, yielding an overall mortality rate of 11.9 (95% CI: 10.0-14.2) per 100 person-years. The risk of death was 2-fold higher in COPD patients than in those with normal airflow (HR 1.97, 95% CI: 1.36-2.84) (Table 2). Adjustment for physical activity did not alter the risk estimates, and neither did further adjustments for BMI, smoking, cancer, history of cardiovascular disease and acute medical conditions.

Patients with COPD stage III/IV had significantly poorer survival after a VTE than those with normal airflow (Figure 1), and 50% of the patients with COPD stage III/IV died within the first 3.5 months. The crude mortality rate increased across stages of COPD from 9.4 per 100 person-years in those with stage I, to 50.7 per 100 person-years in those with stage III/IV (Table 3). The risk of death

was more than 5-fold higher in those with COPD stage III/IV (HR 5.97, 95% CI: 3.29-10.8), compared with those with normal airflow. In those with an initial PE, the relative risk of death was even higher, and patients with COPD stage III/IV had a 7-fold higher risk of death compared with those with normal airflow (HR 7.48, 95% CI: 3.07-18.2). Adjustment for BMI, physical activity, smoking status, cancer, history of cardiovascular disease and acute medical conditions did not alter the risk estimates (Table 3).

Among the VTE patients with severe COPD (stage III/IV), 43.8% had cancer. When we restricted our analyses to patients without active cancer (Supplementary table 1), the HR for death in those with stage III/IV versus normal was 11.4 (95 % CI: 3.4-38.2). The corresponding HR among those with cancer was 4.67 (1.45-15.0). However, the overall number of events in each strata (i.e. with and without cancer) were small, and these estimates should be interpreted with caution.

## **Discussion**

In the present study, we investigated whether COPD, assessed by spirometry, influenced the risk of all-cause mortality in patients with VTE. We found that, VTE patients with concomitant COPD had a 2-fold higher risk of death compared to patients without COPD. The crude mortality rates and relative risks of mortality in VTE patients increased with the severity of COPD. In patients with PE, those with COPD stage III/IV had a 7.3-fold higher risk of death compared to those without COPD. Correspondingly, in DVT patients, the risk of death was 3.8-fold higher in those with COPD stage III/IV. Overall, 50% of the VTE patients with COPD stage III/IV died within the initial 3.5 months. Although the proportion of inactive subjects increased with the severity of COPD, inactivity did not explain the increased mortality in COPD patients. Further, the higher death rate in VTE patients with severe COPD could not be explained by concomitant cancer or history of cardiovascular diseases, as the results remained essentially unchanged when these comorbidities were adjusted for in the multivariable model. Our findings suggest that particular attention and medical care should be



brought to VTE patients with concomitant COPD, and severe COPD in particular, to prevent the high short-term risk of death in these patients.

In coherence with previous studies, we found that VTE patients with concomitant COPD had an almost 2-fold higher mortality risk than those without COPD. In a cohort of 399 PE patients, of whom 95 died within a year, the presence of chronic lung disease (defined by a history of COPD, interstitial lung disease or pulmonary fibrosis on chest radiography) was associated with a 2.2-fold increased risk of death (22). In a study of 2218 VTE cases occurring among Olmsted County residents in the period 1966-1990, chronic lung disease was associated with a 1.4-fold increased risk of both short-term and long-term mortality in multivariable analyses (20). Likewise, Piazza et al. reported that among 2488 VTE patients from the Worcester study, of whom 484 (19.5%) had a history of COPD, concomitant COPD was associated with a 2.0-fold increased risk of death within 30 days after the VTE diagnosis (21). We extend these findings by showing that the impact of COPD on mortality in VTE patients increased with the severity of COPD. VTE patients with concomitant COPD stage III/IV had a 5.3-fold higher mortality risk than those without COPD with a particular steep mortality rate during the first months after VTE diagnosis. Our findings indicate that approximately 60% of VTE patients with concomitant COPD stage III/IV will die during the first year after the VTE diagnosis.

Several mechanisms may underlie the observed impact of COPD on VTE-related mortality. First, COPD patients often suffer from multiple comorbid conditions (20-22), such as arterial cardiovascular diseases, infections and cancer, which may confound the apparent association between COPD and VTE-related mortality. Smoking is associated with both COPD and cancer (35, 36), and active cancer is associated with a 4 to 7-fold increased risk of VTE (37) and a substantial worsening of the VTE prognosis (5, 6). Similarly, COPD is associated with an increased risk of arterial cardiovascular diseases (38), and arterial cardiovascular diseases are associated with a transiently increased risk of VTE (39, 40) and poor prognosis (41). Infection is known to be a provoking factor for VTE (42), and concomitant respiratory infection increases the mortality risk in COPD patients (43).

Moreover, COPD represents a chronic inflammatory state which may influence the risk of adverse outcome (44). In our study, the impact of COPD on VTE-related mortality was neither explained by concomitant cancer, infections, nor arterial cardiovascular diseases since the risk estimates of VTE-related mortality remained essentially unchanged when active cancer, acute medical conditions and a history of MI and stroke were included in the adjustment models. Second, COPD, and particularly severe COPD, is associated with an inactive lifestyle (24, 25, 45) and frequent immobilization during hospitalization (21), which are both detrimental predictors of mortality (21, 26, 27). Even though physical inactivity was associated with increased mortality in the VTE patients, the impact of COPD on VTE-related death was not explained by inactivity since adjustment for inactivity had a minor effect on the risk estimates for death in COPD patients. Third, patients with COPD, of whom many have already developed chronic right ventricular dysfunction, are susceptible to cardiovascular collapse due to superimposed right ventricular failure following symptomatic and asymptomatic PE (46). Unfortunately, we did not have detailed information on heart failure, infections and degree of inflammation, and could therefore not take this into account in our analyses. Of note, the patients with severe COPD had lower BMI than those with normal airflow, a feature recognized in many studies as the “obesity paradox” (47).

The main strengths of the study are the well-validated VTE events derived from a general population cohort, objective assessment of lung function, which allowed for categorization into stages of COPD, possibility to adjust for confounders, and the complete follow-up. Some limitations should also be addressed. The statistical power was somewhat limited in subgroup analysis due to few events, resulting in wide confidence intervals. Therefore, our results should be interpreted with caution. Moreover, COPD is a progressive disease, and the stages of COPD may have changed during follow-up leading to some degree of exposure misclassification. In addition, our spirometry measures were carried out without a test of reversibility, and some subjects with asthma could have been misclassified as having COPD. This potential misclassification would be non-differential, and most likely lead to an underestimation of the true association due to regression dilution bias.

Unfortunately, we did not have information on specific causes of death, and therefore we could not further disentangle the reasons for the increased mortality in VTE patients with COPD.

In conclusion, COPD was associated with a higher risk of death in patients with a first VTE, and this was particularly pronounced among those with severe COPD. Physical inactivity could not explain the increased risk of mortality observed in VTE patients with COPD, indicating that mechanisms other than physical inactivity play a more important role in increasing the risk of death in VTE patients with COPD. Our findings suggest that attention should be drawn to prevention and management of VTE, particularly in patients with severe COPD.

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### **Author contributions**

Conception and design: JBH

Data collection: TB, SKB, HM, JBH

Statistical analyses: TB, SKB, LE

Draft of manuscript: TB, JBH

Interpretation of results: TB, LE, WMM, EBB, HM, SKB, JBH

Critical revision of the manuscript: LE, WMM, EBB, HM, SKB, JBH

### **Conflicts of interest**

The authors report no conflict of interest.

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**Figure legends:**

**Figure 1:** Survival after a first venous thromboembolism (VTE) according to stages of chronic obstructive pulmonary disease (COPD).

**Table 1.** Characteristics of the VTE patients (n=256) across categories of COPD.

	Normal	COPD Stage I	COPD Stage II	COPD Stage III/IV
n	161	35	44	16
Age, years	73.1 ± 9.2	75.2 ± 9.3	75.1 ± 7.0	76.3 ± 5.7
Sex, % men	49.1 (79)	57.1 (20)	54.6 (24)	50.0 (8)
Pulmonary embolism, %	50.3 (81)	60.0 (21)	45.5 (20)	50.0 (8)
Deep vein thrombosis, %	49.7 (80)	40.0 (14)	54.5 (24)	50.0 (8)
Unprovoked VTE	37.9 (61)	34.3 (12)	31.8 (14)	31.3 (5)
BMI, kg/m <sup>2</sup>	28.7 ± 4.3	25.4 ± 3.4	26.3 ± 3.7	25.8 ± 5.3
Current smoking, %	12.5 (20)	22.9 (8)	50.0 (22)	56.3 (9)
Former smoking, %	47.5 (76)	57.1 (20)	40.9 (18)	31.3 (5)
Physical Inactivity (%)	26.7 (43)	22.9 (8)	40.9 (18)	50.0 (8)
Active Cancer, %	31.1 (50)	25.7 (9)	34.1 (15)	43.8 (7)
Cardiovascular disease, %	19.3 (31)	17.1 (6)	27.3 (12)	25.0 (4)
Acute medical conditions, %	12.4 (20)	25.7 (9)	9.1 (4)	18.8 (3)
Dyspnea, %	6.8 (11)	14.3 (5)	13.6 (6)	31.3 (5)
Cough daily, %	13.0 (21)	31.4 (11)	29.6 (13)	50.0 (8)
FEV1, liters	2.6 ± 0.7	2.8 ± 0.7	1.9 ± 0.4	1.1 ± 0.3
FVC, liters	3.5 ± 0.9	4.2 ± 1.1	3.0 ± 0.8	2.2 ± 0.7
FEV1/FVC, %	75.5 ± 3.5	65.4 ± 3.6	62.4 ± 6.9	49.1 ± 9.1
FEV1 % normal	92.0±15.0	94.1±11.3	66.7±8.6	40.3±7.8

Physical inactivity: <1 hour of physical activity per week

Cardiovascular disease: History of myocardial infarction, stroke or angina pectoris

Acute medical conditions: acute myocardial infarction, stroke or major infectious disease within 8 weeks before the VTE.

FEV1: forced expiratory volume in 1 second

FVC: forced vital capacity

**Table 2.** Mortality rates (MR) and Hazard ratio (HR) with 95% confidence intervals (CI) of death in patients with a first venous thromboembolism (VTE) according to chronic obstructive pulmonary disease (COPD).

	Person-years	Deaths	MR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>c</sup>	HR (95% CI) <sup>d</sup>
<b>All VTEs (n=256)</b>						
Normal	702	66	9.4 (7.4-13.2)	Reference	Reference	Reference
COPD	333	57	17.1 (13.2-22.2)	1.97 (1.36-2.84)	1.96 (1.35-2.84)	2.00 (1.30-3.08)
<b>Pulmonary embolism (n=130)</b>						
Normal	329	34	10.3 (7.4-14.5)	Reference	Reference	Reference
COPD	172	27	15.7 (10.8-22.9)	1.48 (0.86-2.56)	1.48 (0.86-2.56)	1.45 (0.73-2.86)
<b>Deep vein thrombosis (n=126)</b>						
Normal	374	32	8.6 (6.05-12.1)	Reference	Reference	Reference
COPD	161	30	18.7 (13.1-26.7)	2.51 (1.48-4.26)	2.65 (1.55-4.51)	2.28 (1.19-4.40)

<sup>a</sup> Per 100 person-years

<sup>b</sup> Adjusted for age (as timescale) and sex

<sup>c</sup> Adjusted for age (as timescale), sex and physical activity

<sup>d</sup> Adjusted for age (as timescale), sex, physical activity, BMI, smoking, active cancer, history of cardiovascular diseases and acute medical conditions.



**Table 3.** Mortality rates (MR) and Hazard ratio (HR) with 95% confidence intervals (CI) of death in patients with a first venous thromboembolism (VTE) according to stages of chronic obstructive pulmonary disease (COPD).

	Person-years	Deaths	MR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>c</sup>	HR (95% CI) <sup>d</sup>
<b>All VTEs (n=256)</b>						
Normal	702	66	9.4 (7.4-12.0)	Reference	Reference	Reference
Stage I	141	15	10.6 (6.4-17.6)	1.22 (0.69-2.15)	1.23 (0.70-2.18)	1.18 (0.63-2.21)
Stage II	161	27	16.7 (11.5-24.4)	1.94 (1.21-3.12)	1.90 (1.18-3.04)	2.23 (1.30-3.85)
Stage III/IV	30	15	50.7 (30.6-84.1)	5.97 (3.29-10.82)	6.04 (3.33-10.9)	5.20 (2.65-10.2)
<b>Pulmonary embolism (n=130)</b>						
Normal	329	34	10.4 (7.4-14.5)	Reference	Reference	Reference
Stage I	79	10	12.7 (6.8-23.5)	1.21 (0.58-2.55)	1.23 (0.59-2.57)	1.08 (0.46-2.51)
Stage II	82	9	11.0 (5.7-21.1)	1.00 (0.45-2.22)	1.00 (0.45-2.23)	1.52 (0.57-4.03)
Stage III/IV	11	8	72.6 (36.3-145)	7.48 (3.07-18.2)	7.91 (3.17-19.8)	7.39 (2.11-25.8)
<b>Deep vein thrombosis (n=126)</b>						
Normal	374	32	8.6 (6.0-12.1)	Reference	Reference	Reference
Stage I	63	5	8.0 (3.3-19.1)	1.10 (0.42-2.88)	1.27 (0.48-3.37)	1.27 (0.42-3.82)
Stage II	79	18	22.7 (14.3-36.0)	3.17 (1.69-5.96)	2.98 (1.59-5.60)	2.91 (1.27-6.64)
Stage III/IV	19	7	37.7 (18.0-79.0)	4.69 (1.93-11.4)	5.72 (2.29-14.3)	3.74 (1.26-11.1)

<sup>a</sup> Per 100 person-years

<sup>b</sup> Adjusted for age (as timescale) and sex

<sup>c</sup> Adjusted for age (as timescale), sex and physical activity

<sup>d</sup> Adjusted for age (as timescale), sex, physical activity, BMI, smoking, active cancer, history of cardiovascular diseases and acute medical conditions.

**Supplementary table 1.** Mortality rates (MR) and Hazard ratio (HR) with 95% confidence intervals (CI) of death according to stages of chronic obstructive pulmonary disease (COPD) in patients with and without cancer-related venous thromboembolism (VTE).

	Person-years	Deaths	MR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>c</sup>	HR (95% CI) <sup>d</sup>
<b>No cancer (n=175)</b>						
Normal	607	25	4.1 (2.8-6.1)	Reference	Reference	Reference
Stage I	133	8	6.0 (3.0-12.0)	1.48 (0.65-3.33)	1.48 (0.66-3.35)	1.09 (0.43-2.81)
Stage II	140	15	10.8 (6.5-17.8)	2.61 (1.31-5.21)	2.53 (1.27-5.03)	2.51 (1.21-5.18)
Stage III/IV	27	8	29.9 (15.0-59.8)	11.2 (4.63-27.2)	11.4 (4.71-27.5)	11.4 (3.40-38.2)
<b>Cancer (n=81)</b>						
Normal	95	41	43.3 (31.9-58.8)	Reference	Reference	Reference
Stage I	9	7	75.3 (35.9-158)	1.22 (0.47-3.17)	1.15 (0.43-3.07)	0.80 (0.28-2.29)
Stage II	22	12	55.0 (31.2-96.8)	1.45 (0.69-3.05)	1.49 (0.70-3.17)	1.56 (0.63-3.90)
Stage III/IV	3	7	245 (117-514)	3.17 (1.15-8.75)	3.37 (1.18-9.61)	4.67 (1.45-15.0)