

D-dimer in COPD out-patients: Distribution, association with mortality and effect modification by anticoagulant therapy.

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Background

D-dimer is a marker for degradation blood clots, and the analysis has a high sensitivity for venous thromboembolisms in low-risk populations¹. D-dimer in a population without known cardiovascular disease is associated with both all-cause mortality and cancer mortality², and in healthy middle-aged adults, baseline D-dimer levels have shown a non-linear association with mortality, where the mortality is increased above 0.21mg/L (equivalent to 0.42mg(FEU)/L). It has been shown that the highest quartile of D-dimer levels predicts all-cause mortality, where persons with a D-dimer level above 0.31mg/L (equivalent to 0.62mg (FEU)/L) have a HR for death of 1.97. Additionally, they performed a test for trend with increasing levels of D-Dimer in the upper quartile, which was significant³. Furthermore, D-dimer can predict the risk of future venous thromboembolism, with an HR of 3.0 comparing the fifth quintile of D-dimers with the first⁴. Chronic obstructive pulmonary disease (COPD) affects approx. 210 mio. people worldwide, and is the cause of nearly 1.9 mio deaths annually⁵. In patients admitted for acute exacerbation of COPD, the patients in the highest D-dimer quartile had a higher risk of in-hospital death and a HR for 1 year mortality of 3.48⁶.

Venous thromboembolic diseases are highly prevalent in COPD patients admitted with acute exacerbation of COPD and are probably underdiagnosed^{7 8}. The distribution of D-dimer levels amongst stable COPD patients has been investigated by a smaller case-control study, which suggested the same levels as in a sex and age-matched population⁹. Thus, the distribution of D-dimer levels

among stable patients with severe COPD warrants investigation in a larger group. Furthermore, it is unknown whether D-dimer levels are associated with all-cause mortality in COPD patients with severe/very severe COPD and whether treatment with anticoagulant therapy might affect this association.

Aims

Primary:

- 1) Describe the distribution of out-patient D-dimer values in severe COPD patients in stable phase, and whether antithrombotic and anticoagulant treatment affects this distribution
- 2) Determine whether D-dimer in the highest quartile is independently associated with all-cause mortality in severe COPD patients.
- 3) Determine whether antithrombotic and anticoagulant treatment affects the association with all-cause mortality of a D-dimer in the highest quartile

Secondary:

- 1) Compare D-dimer values in smokers, former smokers and never smokers.

Hypotheses

- 1) The distribution of D-dimer levels in COPD patients corresponds to that of the healthy population.
- 2) D-dimer in the upper quartile [expected to be approx. above 0.3 mg (FEU)/L] level of normal can independently predict all-cause mortality in COPD patients, when adjustment is done for known predictors of mortality in such patients.
- 3) Anticoagulant and antithrombotic treatment reduces the association of a D-dimer in the highest quartile with all-cause mortality

Data sources

The data will be obtained from the Danish National Patient Registry, which contains information on all admissions to Danish Hospitals and outpatient specialist clinic visits, with diagnosis codes.

This will be linked with the National Laboratory Database, which contains information on laboratory values from four of five Regions of Denmark. All this will furthermore be linked with the Danish Central Person Registry, which includes information on citizens of Denmark, including vital status.

Methods

Study design

Retrospective cohort, registry-based study.

Study period

The observation period starts on the date of the first out-patient D-dimer sample taken on each patient (after 1st of June 2020) and continues until either *i*) death, *ii*) emigration from Denmark, *iii*) until sufficient power has been achieved*, whichever comes first.

* Sufficient power: 336 (252+84) person-years follow-up. Power calculation performed based on following assumptions: Mortality of 5% and 15% with D-dimer levels in the lower $\frac{3}{4}$ and upper $\frac{1}{4}$ quartiles, respectively. Sample allocation ratio 3:1. α : 0.05 and β : 0.80.

Study population

The study population is defined as all COPD patients with a D-dimer sample collected by the outpatient clinic after 1st of June 2020, Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital.

Inclusion criteria

All patients with a registered diagnosis of COPD (ICD-10: DJ44) and an outpatient D-dimer value collected at the outpatient clinic, Section of Respiratory Medicine, Department of Medicine, Herlev and Gentofte Hospital.

Exclusion criteria

- Known malignant disease at the time of inclusion (except non-melanoma malignancies of the skin)
- Known abdominal aortic aneurism or aortic dissection
- Known VTE within 3 months prior to the sample date
- Age < 50 years old (to rule out pregnancy)
- Known parenchymal liver disease
- Surgery within 14 days prior to the sample date
- Significant bleeding episode (i.e. requires hospital contact) within 3 months prior to the study

Outcomes

The study will clarify the D-dimer levels on a selection of out-patient COPD patients.

The primary outcome will be all-cause mortality.

The secondary outcome will be days alive and out of hospital. In-hospital will be defined as any contact with a hospital lasting over 12 hours.

Both primary and secondary outcomes will be examined by comparing the highest quartile of D-dimer levels to the lowest three quartiles.

Statistical analysis

Descriptive statistics will be performed on baseline data, in order to describe the D-dimer levels of patients with severe COPD. Furthermore, the distribution among the subgroup of patients without anticoagulant or P2Y12 inhibitor treatment will be examined. The threshold for the following analysis will be determined by the descriptive statistics, as the aim is to compare the highest quartile to the rest.

All-cause mortality will be examined by an adjusted Cox proportional hazards regression for age and sex, subsequently an adjusted Cox proportional hazards regression, adjusted for age, sex, systemic corticosteroid consumption, ICS (grouped in 4 levels) and CRP. Days alive and out of hospital will be analyzed with either a T-test or Wilcoxon analysis depending on the distribution of data.

For the secondary aim, a comparison of D-dimer levels among smokers, former smokers and never smokers will be performed via T-test.

If D-dimer is shown to be associated with all-cause mortality, the effect of anticoagulant treatment and P2Y12-inhibitor treatment on the association will be examined. Statistical analyses are performed using SAS 9.4 with databases through the Danish Health Data Authority.

Figures and tables

Table 1: Baseline table comparing the patients with D-dimer in the fourth quartile with patients with D-dimer in the lower three fourth of quartiles.

Figure 1: Study flowchart

Figure 2: Kaplan-Meier curve depicting survival based on D-dimer levels

Figure 3: Box and whiskers plot depicting smoking status and D-dimer levels

Publication of results

The study is part of PhD-project for the first author. The results of the study will be published whether they are positive, negative or inconclusive. The publication is planned in international peer-reviewed scientific journals. If publication in a scientific journal is not possible within a reasonable time frame, the results of the study will be published in report format, which will be made available via the Internet.

Ethical statement/approval

The study has been approved by the Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

Name of institution responsible for data

Copenhagen Unit for Respiratory Epidemiology (CURE), Section of Respiratory Medicine, Department of Medicine

Name of project manager

Peter Kamstrup, MD

End date of the project, if any

30th of November, 2027

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