Troponin T elevation and long-term mortality after COPD exacerbation

Short title: Troponin T and mortality in COPD

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ABSTRACT

Background: Patients with chronic obstructive pulmonary disease (COPD) are at increased risk of cardiovascular disease, and exacerbations increase strain on the heart. We have investigated the prognostic value of elevated circulating levels of cardiac troponins seen during COPD exacerbations.

Methods: From the hospital database, 897 patients discharged after treatment for COPD exacerbation in the years 2000-2003 were identified and followed until 30th June 2005. Median observation time was 1.9 years. In 396 patients, measurements of cardiac-specific Troponin T (cTnT) were available. Levels of cTnT $\geq 0.04\mu$g/L were considered elevated. Clinical data were retrieved from patient records. Date of death was obtained from the Central National Registry. To balance the non-randomised nature of available cTnT measurements, an exposure propensity score (EPS) for cTnT sampling was calculated, and used in regression analyses.

Results: After adjusting for EPS in Cox regression analyses, elevated cTnT was significantly associated with increased all-cause mortality in the observation period, with an HR of 1.64 (95% confidence interval: 1.15-2.34).

Conclusion: COPD patients with cTnT elevation during exacerbation are at increased risk of death after discharge.

Chronic obstructive pulmonary disease (COPD) is a common and debilitating disease, characterised by airflow limitation that is not fully reversible and usually progressive [1]. This disease represents an increasing health burden worldwide, and is the only leading cause of death that still has a rising mortality rate in industrialised countries [2]. The most important risk factor for COPD is smoking, and the majority of patients are former or current smokers [1,3]. Thus, this patient population has an increased likelihood of developing other smoking-related diseases, including ischemic heart disease (IHD) [4,5]. In a recent review article on the role of comorbidities in COPD, the authors conclude that cardiovascular disease is a major cause of death in COPD. Although the underlying mechanisms are not fully understood, this could be due to chronic systemic and pulmonary inflammation [6].

Many COPD patients experience periods of disease exacerbation, with increased dyspnea, sputum secretion, chest tightness and cough [7]. During exacerbations, bronchoconstriction and mucus production, alveolar hypoxia and resultant elevation of pulmonary vascular resistance can lead to hypoxemia and increased heart rate. Consequently, exacerbations represent an increased burden to the heart, and myocardial injury with release of cTnT may occur.

Still, the literature on troponins in COPD exacerbations is sparse. Searching Medline and Embase databases, we were only able to identify one single study on the prevalence of cTnT elevation in patients hospitalised for COPD exacerbation [8], and one study examining the in-hospital prognostic value of cardiac troponin I (cTnI) elevation among COPD patients admitted to an intensive care unit (ICU) [8,9]. Accordingly, the objective of this study was to explore the long term prognostic value of elevated cTnT seen during COPD exacerbation.

METHODS

The study population consisted of a historic cohort of patients discharged from Akershus University Hospital, a 700-bed teaching hospital that serves suburban and countryside regions, after treatment for COPD exacerbation. Cases were identified using the hospital's patient database. Patients aged 40 years or older who were admitted during the four year period 1 January 2000 – 31 December 2003, and were discharged with a primary diagnosis of COPD exacerbation, ICD 10 (International Classification of Diseases, 10th revision) code J44.0 or J44.1, or COPD (J44.x) as an underlying diagnosis combined with pneumonia (J13-J18.9) as the main diagnosis, were included. The choice of study period was based on data availability, as changes in hospital database software made it harder

to retrieve complete data from outside this time period. For patients with more than one admission during the inclusion period, the latest admission date was used. They were followed until death or 30 June 2005, whichever occurred first. Patients with previous diagnoses of sarcoidosis, interstitial lung disease, or neuromuscular disease were excluded. In all, 897 patients met the inclusion criteria.

Mortality data were gathered from the Central National Register, which is based on a unique personal identification number for all Norwegian inhabitants.

Results of laboratory analyses performed within 24 hours from the time of hospital admission were retrieved from the hospital's laboratory database. If multiple results were available, average hemoglobin concentrations (Hb), maximum white blood cell count (WBC), cTnT and C-reactive protein (CRP), and minimum creatinine values were used. CRP levels were measured by a immunoturbidimetric method, Cobas Integra (Roche Diagnostics GmbH, Mannheim, Germany), and the cTnT assay used by the hospital laboratory was Elecsys Troponin T STAT (Roche Diagnostics GmbH, Mannheim, Germany). Our laboratory reported cTnT levels as measureable if equal to or greater than 0.01 μg/L, and elevated at levels equal to or greater than 0.04 μg/L, at which point the assay has less than 10% coefficient of variation (personal communication with laboratory).

Patient data from emergency room presentation, including oxygenation measured by pulse oximetry, supplemental oxygen flow, arterial blood gas analysis (pO_2, pCO_2, pH), blood pressure, heart rate, heart rhythm and respiratory frequency, in addition to medication use on admission and at discharge, were manually gathered from hospital records.

All diagnostic discharge ICD codes entered for each patient since 1987, until but not including the date of admission, were obtained from the hospital database. For each patient, groups of codes were used to construct a history of lung cancer, other cancers, diabetes, hypertension, IHD, congestive heart failure, atrial fibrillation, cerebrovascular disease, peripheral vascular disease and venous thromboembolism.

Patients were considered to have established IHD if there existed a previous diagnosis of myocardial infarction, hospitalisation for unstable angina, or they had undergone percutaneous coronary intervention or coronary artery bypass surgery.

Spirometry data, if performed in a stable state at least one week before hospital admission or four weeks after discharge, were gathered from patient records. Forced vital capacity (FVC), expiratory volume in one second (FEV$_1$), height and weight were recorded, and body mass index (BMI), defined as weight in kilograms divided by the square of height in meters, was calculated. FVC and FEV$_1$ values are expressed as percent of predicted using the European Community for Steel and Coal equations.[10]

Available chest X-ray (CXR) images from the date of admission were re-examined in co-operation by two physicians (VS and SHH), who were blinded regarding clinical data. The following parameters were evaluated: Cardiomegaly, hyperinflation, pneumonic infiltrates, and pulmonary congestion.

The study was approved by The Data Inspectorate, and reviewed by the Regional Committee for Research Ethics.

Statistical analyses

All-cause mortality was used as the outcome measure. Continuous covariates were dichotomised; creatinine, heart rate and oxygen saturation at the 10th/90th percentile, pCO$_2$, FEV1 % of predicted and BMI at the 25th/75th percentile, and WBC count and CRP at the median. cTnT concentration was stratified at 0.01 and 0.04 µg/L for regression analyses.

First, baseline differences between patients with and without cTnT measurements were compared using univariate methods (t-test or chi-square as appropriate).

Second, variables with a p-value less than or equal to 0.15 in the univariate analyses, and/or deemed to be potentially associated with the decision to measure cTnT were entered into a logistic regression model. This model was then used to to calculate individual exposure propensity scores (EPS) for the probability of cTnT measurement [11].

Third, age- and gender-adjusted relative mortality was assessed using Mantel-Haenszel test for incidence density data.

Fourth, all covariates having a significance level of 0.15 or lower in the stratified analyses were entered into a Cox proportional hazards models for all-cause mortality. Models for the subgroup with cTnT measurement and for the full cohort were compared, using EPS as a balancing score.

Finally, we applied the same Cox models to more restricted cohorts, excluding patients with lung cancer, ischemic heart disease, and never smokers.

Time since discharge was used as the underlying time variable. The proportional hazard assumption was tested using traditional log-log plots and Schoenfeld's residuals on partial likelihood [12]. Results are reported as odds ratio (OR) for logistic regression models, and hazard ratio (HR) for Cox analyses, with 95% confidence intervals in parentheses.

All statistical analyses were performed using Stata/SE version 8.2 software (StataCorp LP, Texas, USA). Propensity scores were calculated using the **pscore** program module for Stata, version 2.02, by Becker and Ichino.

RESULTS

Mean age at discharge was 70.9 years, and 50.8% were female. Only 55 (6%) of the patients had never smoked. Spirometry data was available for 697 patients. Out of these, 608 (87%) had an FEV_1/FVC-ratio ≤ 0.7. cTnT had been measured in 396 patients. The median time of observation was 1.9 years. After discharge, cumulative survival was 75.6% and 65.2% at one and two years, respectively.

In univariate analysis, there was a slight difference in survival (HR 1.25 (1.01-1.54), p=0.04, Cox regression) between patients who had had cTnT measured and those who had not (figure 1). However, adjusting for EPS, which assigns a probablity of sampling to each patient, the mortality risk was nearly equalised and statistically non-significant (HR 1.12 (0.90-1.39), p=0.33, Cox regression) (figure 2). There was a highly significant difference in overall survival (p<0.0001, age-stratified log rank) between patients with versus without cTnT elevation, and an equally significant trend for mortality as a function of cTnT concentration when stratified (figure 3).

Baseline characteristics for the groups with and without cTnT measurements are presented in table 1. The covariates associated with cTnT measurement for the full cohort, and thus included in the calculation of the EPS, are presented with odds ratios for measurement. Patients with reduced FEV_1 or hyperinflation on X-ray had a lower probability of cTnT sampling, whereas a history of ischemic heart disease, use of aspirin, or CXR signs of pulmonary congestion increased the odds of cTnT measurement.

cTnT was at a measureable level in 173 of the 396 samples, median concentration was 0.04μg/L, the 95th percentile was 0.28μg/L. The patients with elevated cTnT presented with higher WBC and

creatinine, and had slightly worse pulmonary function. Cardiomegaly was more common among those with elevated cTnT, whereas infiltrates were more often seen in patients without cTnT elevation.

Hypertension, low pH, elevated C-reactive protein, signs of infiltrate or hyperinflation on CXR, and use of beta-adrenergic blockers, angiotensin converting enzyme inhibitors, warfarin or aspirin were covariates initially tested in stratified analyses which did not have an association with mortality at a p-value less than 0.15, and thus were not included in the regression models.

Table 2 shows two multivariate Cox survival models; one for the subgroup of patients with cTnT measurement, and one for the entire cohort. The same variables are used in both models, with the addition of EPS as a balancing score in the full cohort model, to adjust for the potential bias in the selection of patients.

In the regression analyses, several covariates had a significant positive association with mortality, with cTnT elevation, old age, anemia, reduced FEV_1, low BMI, low oxygen saturation, cardiomegaly and history of ischemic heart disease, thromboembolism or cancer among the major contributors, whereas never smokers and statin users had a reduced mortality risk. Removing EPS from the full cohort model resulted in only a modest change in the HR for cTnT $\geq 0.04\mu g/L$ to 1.61 (1.13-2.29).

Since cTnT concentration was highly skewed, a log transformed variable was generated and substituted for the stratified cTnT variable used in the models in table 2. The association with mortality was highly significant, with a hazard ratio per standard deviation for log(cTnT) of 1.24 (1.04 – 1.47) for the cTnT subgroup.

Patients with ischemic heart disease, lung cancer and never smokers were then sequentially excluded from the models in table 2. The adjusted HRs for cTnT are presented in table 3. In all of the reduced models, elevated cTnT remained significantly associated with increased mortality risk for the full cohort, but only marginally significant in the subgroup model. The HRs did not change appreciably between any of the smaller models.

Six patients received a secondary diagnosis of acute myocardial infarction during the index admission. Excluding these patients from the analysis did not have any meaningful influence on the results.

None of the models violated the proportional hazard assumption.

DISCUSSION

We found that elevated cTnT seen during hospitalisation for COPD exacerbation was a strong and independent prognostic factor for mortality after discharge, even after adjusting for multiple well-known determinants of mortality. To the best of our knowledge the association between troponin elevation and mortality in patients discharged from hospital after a COPD exacerbation is a novel finding. Moreover, it may be important for risk stratification and treatment of patients hospitalised for COPD exacerbation.

One obvious limitation of this study is the selection of patients from whom cTnT was sampled. Of the 897 COPD patients in the initial cohort, the physicians on call decided to analyse cTnT in 396. According to hospital guidelines at the time of the study, troponin T testing was recommended in all patients with chest pain and clinical suspicion of acute coronary syndromes. In addition, troponin T testing was mentioned as an option in patients with clinical suspicion of myocarditis, acute heart failure and pulmonary embolism. The non-randomised selection may introduce a bias in the effect estimate, even though the unadjusted comparison of survival of patients with cTnT measurements to those without showed only a very small difference in survival between the two groups. However, by adjusting for a propensity score, EPS, that assigns a probability of cTnT sampling to all 897 patients in the cohort, the survival difference is almost completely equalised and statistically non-significant. Propensity scores have been shown to remove or considerably reduce bias in background covariates, albeit at the cost of reduced statistical power [11,13]. Adding or removing EPS from the final Cox model caused only marginal changes in the HR estimates for cTnT. Thus, we believe the selection of patients for cTnT measurement did not influence the association between cTnT and mortality among these patients. Still, the conclusions drawn from our study should be considered as hypothesis generating.

Excluding subgroups of patients with lung cancer, established IHD, or never smokers from the analysis minimally affected the HR estimates for cTnT elevation in any model. cTnT remained a significant predictor of mortality risk in the full cohort models, but caused the association to be only

borderline significant in the cTnT subgroup models. We ascribe this effect partly to loss of statistical power and partly to patient selection.

As to other markers of myocardial injury, our hospital laboratory did not offer cTnI analysis in the time period of this study, but cTnI is likely to have yielded similar results. The inferior signal to noise ratio of MB isoform of creatine kinase (CK-MB) analyses may have resulted in reduced ability to identify patients at increased risk. Of the very few patients from whom CK-MB was sampled, all of them had cTnT measured as well.

Using the latest admission date was an arbitrary decision made during data gathering. Since the choice of inclusion date could not influence neither the population sample nor the number of deaths, we believe the effect on the results is marginal.

Long term oxygen therapy (LTOT) has been shown to improve survival in select groups of COPD patients with hypoxemia. Since hypoxic patients may be more vulnerable to myocardial injury, adherence to guidelines for LTOT could possibly influence the association between cTnT and mortality. While we believe that recommendations for LTOT were adhered to during the study period, we do not have exact data on LTOT in our cohort.

Three major alternative explanations for cTnT elevation should be considered in this patient population. Firstly, physicians caring for the patients may have overlooked other conditions that are known to cause troponin elevation, such as pulmonary embolism, renal failure or heart failure [14,15]. Pulmonary embolism is not infrequent as a cause of dyspnea in COPD patients [16], but the diagnosis remains elusive in clinical practice. We included history of thromboembolic disease in our analyses in an effort to control for embolism as a co-factor. Furthermore, serum creatinine was included to adjust for renal function. The study by Baillard and associates reporting increased in-hospital mortality in COPD exacerbations requiring ICU treatment has been criticised for not taking markers of acute heart failure into account [17]. Our hospital laboratory did not provide analysis of B-type natriuretic peptide (BNP) at the time of the study. In order to account for acute pulmonary congestion, we have re-evaluated CXRs to provide an index of acute pulmonary congestion. Information on cephalisation obtained from CXR has been shown to correlate strongly with acute congestive heart failure severity [18].

Secondly, a COPD exacerbation could in itself cause sufficient strain on the heart to cause myocardial cell necrosis. Oedema, mucus hypersecretion and bronchoconstriction may cause further ventilation impairment, and alveolar hypoxia may cause constriction of pulmonary arterioles and increased pulmonary artery pressure, disturbing perfusion. Additionally, respiratory muscle fatigue and abnormal respiratory patterns further deteriorate arterial blood gases. Tachycardia, hypoxaemia, and dilatation of the right ventricle often seen in COPD exacerbations, and complications such as pulmonary arterial hypertension, are all factors that may cause troponin release [14,19].

Thirdly, there is increasing awareness of IHD as a major contributor to morbidity and mortality in this patient population [5,6,20,21]. The majority of patients are current or former smokers, and are at increased risk of developing other smoking-related diseases. While troponin release is seen in COPD even in patients with normal coronary arteries on angiography [15], this does not preclude the possibility that many COPD patients actually have underlying quiescent IHD. If the coronary circulation is already impaired, the extra strain put on the heart by a COPD exacerbation could lead to an oxygen supply-demand mismatch, causing myocardial damage.

Finally, the increased inflammatory response in COPD exacerbations [3,22] may amplify the inflammatory processes associated with atherosclerosis and atherothrombosis [6,23]. We have previously published a paper suggesting a survival benefit of statin treatment in COPD [24], an effect which may be linked to the pleiotropic anti-inflammatory effect of statins.

The diagnosis of COPD in this study was made at discharge, based on all available clinical data. Frequently, deciding whether or not COPD exacerbations are accompanied by pneumonia is difficult. Thus, we included patients coded with pneumonia as the main diagnosis and COPD as the underlying diagnosis. A physician specialised in internal medicine or pulmonary medicine verified the diagnoses. While the diagnosis was not based on specific criteria such as suggested by the Global initiative for chronic Obstructive Lung Disease (GOLD), we consider the study population to be well defined, and representative of COPD patients seen in pulmonary care units in Western countries [1].

The proper and correct coding of causes of death in COPD is difficult, and death certificates may both under- and overestimate COPD and comorbidities as underlying causes of death, causing serious misclassification [6,20]. Thus, we chose all-cause mortality as the outcome measure. The overall MR in our study was comparable with the long-term MR in previous studies of patients hospitalised with COPD exacerbation [25,26]. Thanks to the unique personal identification number

assigned to all Norwegian inhabitants, linkage between registries was possible, allowing mortality data to be gathered from the Central National Register. This ensured complete follow-up of the cohort, and makes misclassification of the outcome highly unlikely.

In conclusion, assessment of cTnT in patients with COPD exacerbation on hospital admission permits identification of patients at increased risk of later death. Considering the dearth of COPD treatments that actually have an impact on prognosis, and the likelihood that at least some of the patients with elevated troponins have treatable but undiagnosed comorbidities, our findings provide an impetus to further characterise the pathophysiologic correlates and determinants of troponin elevation in COPD.

REFERENCES

1 Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256-1276.

2 Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *The Lancet* 1997;349:1498-1504.

3 Barnes PJ. Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2000;343:269-280.

4 Hole DJ, Watt GCM, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 1996;313:711-715.

5 Vollset SE, Tverdal A, Gjessing HK. Smoking and Deaths between 40 and 70 Years of Age in Women and Men. *Ann Intern Med* 2006;144:381-389.

6 Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245-1257.

7 Currie GP, Wedzicha JA. Acute exacerbations. *BMJ* 2006;333:87-89.

8 Harvey MG, Hancox RJ. Elevation of cardiac troponins in exacerbation of chronic obstructive pulmonary disease. *Emerg Med Australas* 2004;16:212-215.

9 Baillard C, Boussarsar M, Fosse JP, Girou E, Le Toumelin P, Cracco C, Jaber S, Cohen Y, Brochard L. Cardiac troponin I in patients with severe exacerbation of chronic obstructive pulmonary disease. *Intensive Care Med* 2003;29:584-589.

10 Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung-Volumes and Forced Ventilatory Flows - Report Working Party Standardization of Lung-Function Tests European-Community for Steel and Coal - Official Statement of the European Respiratory Society. *Eur Respir J* 1993;6:5-40.

11 D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med* 1998;17:2265-2281.

12 Validation of the proportional hazard models. In: Marubini E, Valsecchi MG, eds. *Analysing Survival Data from Clinical Trials and Observational Studies*. West Sussex, England: John Wiley & Sons, Ltd 1995:251-254.

13 Sturmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Analytic Strategies to Adjust Confounding using Exposure Propensity Scores and Disease Risk Scores: Nonsteroidal Antiinflammatory Drugs and Short-term Mortality in the Elderly. *Am J Epidemiol* 2005;161:891-898.

14 Korff S, Katus HA, Giannitsis E. Differential diagnosis of elevated troponins. *Heart* 2006;92:987-993.

15 Mahajan N, Mehta Y, Rose M, Shani J, Lichstein E. Elevated troponin level is not synonymous with myocardial infarction. *Int J Cardiol* 2006;111:442-449.

16 Tillie-Leblond I, Marquette CH, Perez T, Scherpereel A, Zanetti C, Tonnel AB, Remy-Jardin M. Pulmonary Embolism in Patients with Unexplained Exacerbation of Chronic Obstructive Pulmonary Disease: Prevalence and Risk Factors. *Ann Intern Med* 2006;144:390-396.

17 Joffe A. Comments on elevated cardiac troponin in patients with COPD. *Intensive Care Med* 2004;30:732.

18 Knudsen CW, Omland T, Clopton P, Westheim A, Abraham WT, Storrow AB, McCord J, Nowak RM, Aumont MC, Duc P. Diagnostic value of B-Type natriuretic peptide and chest radiographic findings in patients with acute dyspnea. *Am J Med* 2004;116:363-368.

19 Torbicki A, Kurzyna M, Kuca P, Fijalkowska A, Sikora J, Florczyk M, Pruszczyk P, Burakowski J, Wawrzynska L. Detectable Serum Cardiac Troponin T as a Marker of Poor Prognosis Among Patients With Chronic Precapillary Pulmonary Hypertension. *Circulation* 2003;108:844-848.

20 Hansell AL, Walk JA, Soriano JB. What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *Eur Respir J* 2003;22:809-814.

21 Sin DD, Man SFP. 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.

22 Wouters EFM. Local and Systemic Inflammation in Chronic Obstructive Pulmonary Disease. *Proc Am Thorac Soc* 2005;2:26-33.

23 Hansson GK. Inflammation, Atherosclerosis, and Coronary Artery Disease. *N Engl J Med* 2005;352:1685-1695.

24 Soyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. *Eur Respir J* 2007;29:279-283.

25 Almagro P, Calbo E, Ochoa de Echaguen A, Barreiro B, Quintana S, Heredia JL, Garau J. Mortality After Hospitalization for COPD. *Chest* 2002;121:1441-1448.

26 Groenewegen KH, Schols AMWJ, Wouters EFM. Mortality and Mortality-Related Factors After Hospitalization for Acute Exacerbation of COPD. *Chest* 2003;124:459-467.

FIGURE LEGENDS

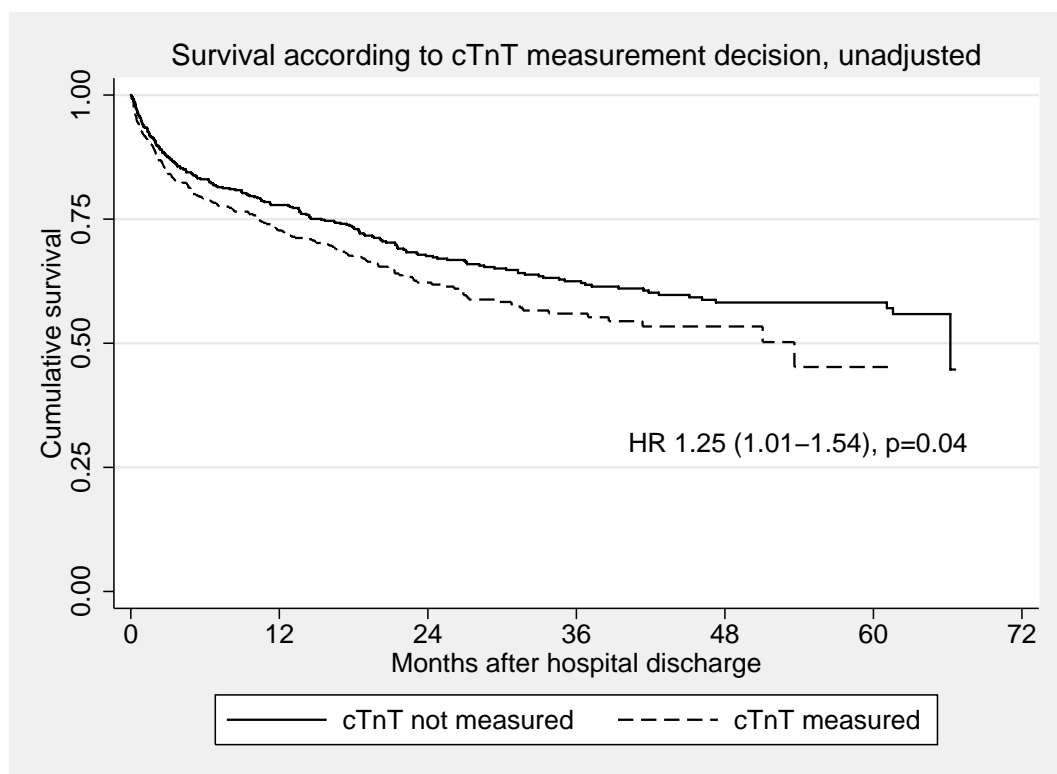Figure 1. Unadjusted Kaplan-Meier survival curve for measured versus not measured cTnT.

Figure 2. Kaplan-Meier survival curve for measured versus not measured cTnT, adjusted for EPS.
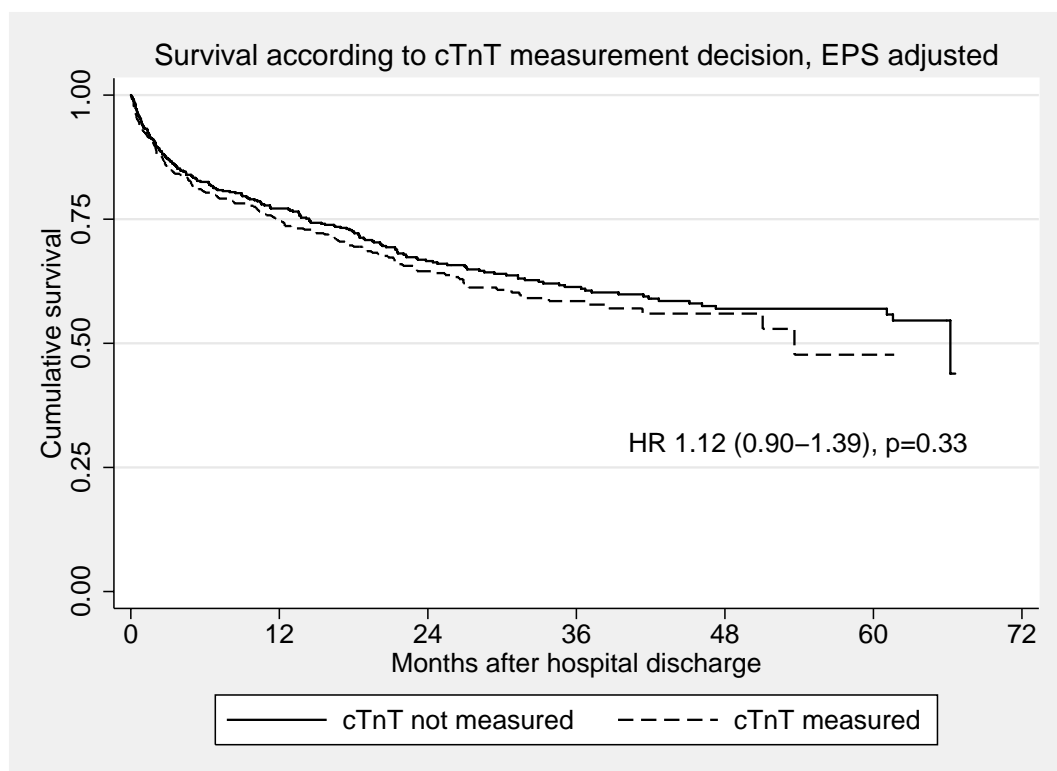
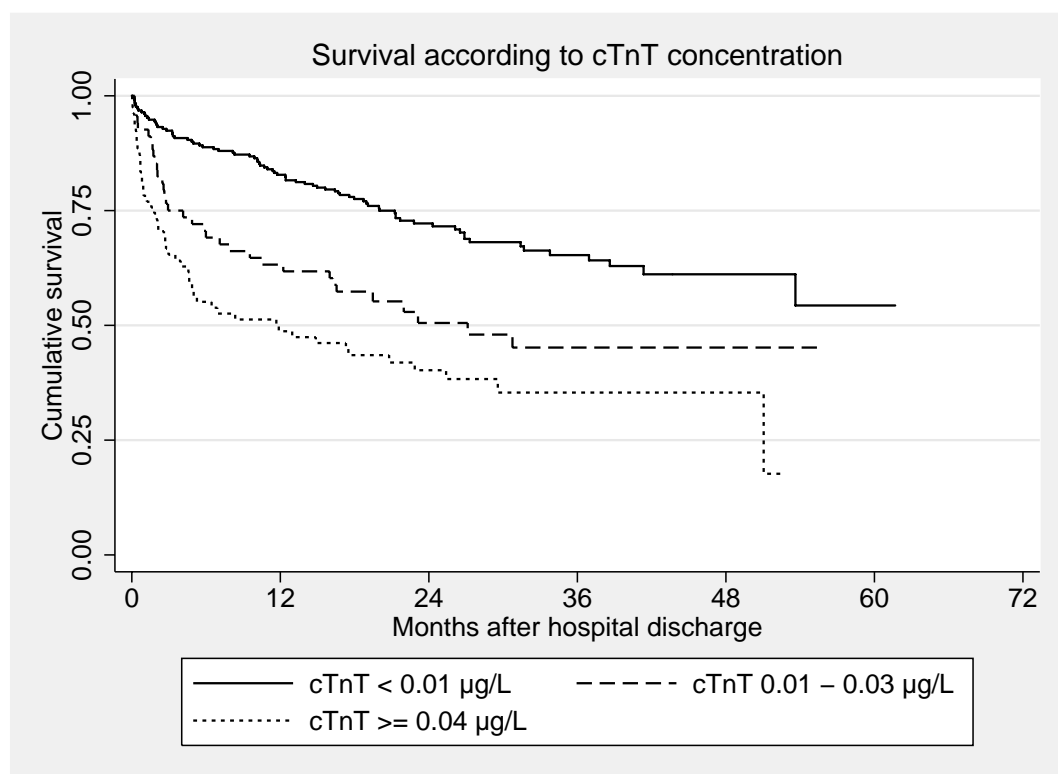Figure 3. Kaplan-Meier survival curve for cTnT concentration strata.

Table 1. Baseline characteristics for all patients, subdivided by cTnT measurement; number of patients (percent), adjusted odds ratio for cTnT measurement (95% confidence interval) and corresponding p-value from multivariate logistic regression model [*]

Characteristic	cTnT measured (n=396)	cTnT not measured (n=501)	Odds Ratio (95% CI)	p-value
Age and gender				
40-59 years	61 (15)	100 (20)		
60-69 years	77 (19)	112 (22)		
70-79 years	142 (36)	186 (37)		
≥ 80 years	116 (29)	103 (21)		
Age + 10 years			1.02 (0.89-1.18)	0.77
Female	197 (50)	259 (52)	0.95 (0.72-1.27)	0.75
Laboratory values[*]				
Creatinine ≥ 120 μmol/l	48 (12)	49 (10)		
Anemia [†]	133 (34)	154 (31)		
WBC ≥ $10 \times 10^6 \times ml^{-1}$	224 (57)	253 (51)		
CRP ≥ 50 mg/l	197 (59)	264 (53)		
Clinical data				
FEV_1 < 30% of predicted	42 (11)	92 (18)	0.59 (0.38-0.91)	0.016
Heart rate ≥ 120 beats/min	63 (16)	98 (20)	0.79 (0.55-1.15)	0.23
Respiratory rate ≥ 30/min	59 (15)	57 (11)	1.38 (0.91-2.10)	0.13
Oxygen saturation < 80 %	16 (4)	29 (6)	0.78 (0.39-1.56)	0.48
Supplemental oxygen	142 (36)	139 (28)	1.37 (1.00-1.86)	0.048
pCO_2 > 6.5 kPa	69 (17)	103 (21)	0.81 (0.55-1.19)	0.28
BMI < 20 kg/m^2	64 (16)	102 (20)	1.02 (0.69-1.51)	0.93
Atrial fibrillation	46 (12)	45 (9)	1.10 (0.68-1.76)	0.71
Chest X-ray				
Cardiomegaly	158 (40)	160 (32)	0.99 (0.72-1.37)	0.97
Congestion (any sign)	121 (31)	101 (20)	1.69 (1.20-2.37)	0.003
Hyperinflation	116 (29)	118 (37)	0.77 (0.56-1.06)	0.11
Medical history				
Ischemic heart disease	150 (38)	107 (21)	1.73 (1.23-2.44)	0.002
Heart failure	47 (12)	42 (8)	0.92 (0.56-1.52)	0.76
Diabetes	61 (15)	48 (10)	1.39 (0.90-2.15)	0.14
Thromboembolism	11 (3)	11 (2)	1.19 (0.48-2.97)	0.71
Cancer	55 (14)	55 (12)	1.12 (0.74-1.71)	0.59
Never smoker	30 (8)	25 (5)	1.34 (0.75-2.42)	0.32
Treatment				
Statins	66 (17)	50 (10)	1.16 (.074-1.80)	0.53
Aspirin	128 (32)	99 (20)	1.54 (1.08-2.18)	0.016
Inhaled corticosteroids	236 (60)	295 (59)	1.09 (0.82-1.46)	0.56

[*] All listed variables except laboratory values were included in the logistic regression model forming the basis for EPS calculation

[†] Hemoglobin concentration < 12 mg/dl if female, Hb < 13 mg/dl if male

WBC – White Blood Cell count; CRP – C-Reactive Protein; FEV_1 – Forced Expiratory Volume in 1 second; BMI – Body Mass Index

Table 2. Hazard ratio (HR) with 95% confidence interval (95% CI) from multivariate Cox regression[*], with corresponding p-value, by characteristic, for the subgroup with cTnT measurement and the full cohort.

	cTnT measured (n=396)			All patients (n=897)		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Age and gender						
Age + 10 years	1.57	(1.29-1.92)	<0.001	1.64	(1.44-1.86)	<0.001
Female	0.82	(0.57-1.19)	0.30	0.83	(0.66-1.04)	0.11
Laboratory values						
Troponin T not measured	-	-	-	1	-	-
Troponin T < 0.01 μmol/l	1	-	-	1.02	(0.78-1.35)	0.86
Troponin T 0.01- 0.03 μmol/l	1.23	(0.78-1.93)	0.38	1.16	(0.79-1.71)	0.45
Troponin T ≥ 0.04 μmol/l	1.66	(1.07-2.56)	0.023	1.64	(1.15-2.34)	0.006
Creatinine ≥ 120 μmol/l	1.48	(0.95-2.32)	0.08	1.25	(0.91-1.71)	0.17
Anemia [†]	1.29	(0.91-1.84)	0.15	1.29	(1.02-1.63)	0.035
WBC ≥ 10 × 106 × ml-1	1.08	(0.76-1.52)	0.68	1.03	(0.83-1.29)	0.77
Clinical data						
FEV1 < 30% of predicted	2.33	(1.40-3.88)	0.001	1.87	(1.27-2.76)	0.001
Heart rate ≥ 120 beats/min	0.95	(0.60-1.51)	0.84	1.2	(0.89-1.63)	0.23
Oxygen saturation < 80 %	2.13	(1.03-4.41)	0.042	2.61	(1.71-3.98)	<0.001
Supplemental oxygen	1.34	(0.95-1.87)	0.09	1.42	(1.09-1.85)	0.009
pCO2 > 6.5 kPa	1.22	(0.78-1.93)	0.39	1.31	(0.98-1.75)	0.07
BMI < 20 kg/m2	1.72	(1.13-2.63)	0.012	1.48	(1.13-1.95)	0.005
Atrial fibrillation	0.98	(0.60-1.59)	0.92	1.4	(1.03-1.90)	0.03
Chest X-ray						
Cardiomegaly	1.72	(1.18-2.49)	0.005	1.42	(1.11-1.83)	0.005
Congestion (any sign)	0.7	(0.48-1.01)	0.06	0.79	(0.57-1.10)	0.16
Medical history						
Ischemic heart disease	1.36	(0.96-1.94)	0.08	1.54	(1.05-2.26)	0.026
Heart failure	1.38	(0.87-2.18)	0.17	1.26	(0.91-1.75)	0.16
Diabetes	1.83	(1.21-2.77)	0.004	1.99	(1.42-2.79)	<0.001
Thromboembolism	1.36	(0.57-3.24)	0.49	1.51	(0.85-2.67)	0.16
Lung cancer	5.63	(3.24-9.81)	<0.001	5.47	(3.66-8.19)	<0.001
Other cancers	2.81	(1.72-4.61)	<0.001	2.38	(1.71-3.31)	<0.001
Never smoker	0.57	(0.29-1.12)	0.11	0.6	(0.35-1.04)	0.07
Treatment						
Statins	0.56	(0.31-1.01)	0.054	0.6	(0.39-0.92)	0.018
Inhaled corticosteroids	0.9	(0.64-1.26)	0.53	0.87	(0.69-1.09)	0.22
EPS	-	-	-	0.5	(0.07-3.53)	0.48

[*] HRs given are adjusted for all other variables in the table

[†] = Hemoglobin concentration < 12 mg/dl if female, < 13 mg/dl if male

WBC – White Blood Cell count; FEV$_1$ – Forced Expiratory Volume in 1 second; BMI – Body Mass Index; EPS – Exposure Propensity Score

Table 3. Sensitivity analyses. Multivariate Cox regression models as in table 2, with different subgroups excluded from the analyses. Hazard ratio (HR) with 95% confidence interval (95% CI) for cTnT, adjusted for all variables in table 2, except as excluded in each model.

	cTnT measured			All patients		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Never smokers exluded						
Troponin T not measured	-	-	-	1	-	-
Troponin T < 0.01 µmol/l	1	-	-	1.07	(0.81-1.41)	0.64
Troponin T 0.01- 0.03 µmol/l	1.07	(0.66-1.75)	0.77	1.07	(0.71-1.62)	0.74
Troponin T ≥ 0.04 µmol/l	1.54	(0.97-2.44)	0.07	1.62	(1.12-2.34)	0.01
Ischemic heart disease exluded						
Troponin T not measured	-	-	-	1	-	-
Troponin T < 0.01 µmol/l	1	-	-	1.04	(0.73-1.47)	0.84
Troponin T 0.01- 0.03 µmol/l	1.13	(0.62-2.07)	0.68	1.07	(0.63-1.80)	0.81
Troponin T ≥ 0.04 µmol/l	1.56	(0.83-2.94)	0.16	1.7	(1.01-2.86)	0.047
Lung cancers exluded						
Troponin T not measured	-	-	-	1	-	-
Troponin T < 0.01 µmol/l	1	-	-	1.05	(0.79-1.40)	0.75
Troponin T 0.01- 0.03 µmol/l	1.28	(0.78-2.10)	0.32	1.2	(0.79-1.81)	0.40
Troponin T ≥ 0.04 µmol/l	1.54	(0.96-2.48)	0.07	1.56	(1.06-2.29)	0.023