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Systemic inflammation induced by exacerbation of COPD or pneumonia in patients with COPD induces cardiac troponin elevation

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ABSTRACT

Background Troponin is a biomarker of myocardial injury. In chronic obstructive pulmonary disease (COPD), troponin is an important determinant of mortality after acute exacerbation. Whether acute exacerbation of COPD (AECOPD) causes troponin elevation is not known. Here, we investigated whether troponin is increased in AECOPD compared to stable COPD.

Methods We included 320 patients with COPD in the stable state and 63 random individuals from Akershus University hospital's catchment area. All participants were ≥40 years old (mean 65·1 years, SD 7·6) and 176 (46%) were females. The geometric mean of high-sensitivity cardiac troponin T (hs-cTnT) was 6·9 ng/L (geometric-SD 2·6). They were followed regarding hospital admission for the subsequent 5 years.

Results During the 5-year follow-up, we noted 474 hospitalisations: Totally, 150 and 80 admissions were due to AECOPD or pneumonia, respectively. The geometric mean ratio with geometric SE (GSE) between cTnT at admission and stable state in AECOPD and pneumonia was 1·27 (GSE=1.11, p=0·023) and 1·28 (GSE=1.14, p=0·054), respectively. After inclusion of blood leucocyte count and C reactive protein at hospitalisation, these ratios attenuated to zero. However, we estimated an indirect of AECOPD and pneumonia on the ratio between hs-cTnT at admission and the stable state to 1·16 (p=0·022) and 1·22 (p=0·008), representing 91% (95% CI 82% to 100%) and 95% (95% CI 83% to 100%) of the total effects, respectively.

Conclusion AECOPD and pneumonia in patients with COPD is associated with higher cTnT levels. This association appears to be mediated by systemic inflammation.

Key messages

- Cardiac troponin increases in chronic obstructive pulmonary disease (COPD) exacerbation.
- Cardiac troponin is increased in exacerbation and pneumonia in COPD. This increase is mediated by systemic inflammation that accompanies exacerbation and pneumonia in COPD.
- Airways inflammation triggers a systemic inflammation that damages the heart muscles.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by an irreversible limitation of airflow that is usually progressive.[1] A large proportion of patients experience periods with acute exacerbation of COPD symptoms (AECOPD) frequently triggered by airway infections and characterised by local airway and/or systemic inflammation.[2 3] COPD is also accompanied by several comorbidities that may represent major health problems for patients. In particular, cardiovascular diseases are common and associated with increased mortality in patients with COPD.[4–7] Previous studies have shown that a circulatory marker of myocardial damage, cardiac troponin (cTn), is an independent prognostic marker of mortality in the general population, in patients with stable COPD, and after AECOPD.[8–10] The level of cTn has been shown to be inversely related to COPD severity as assessed by spirometry in the stable state.[8 10–14] Moreover, the level of cTn has been reported to be higher in patients hospitalised for AECOPD than in patients with COPD in the stable state.[15 16] However, prospective studies that examine the trajectory of cTn during the course of COPD are lacking, and whether myocardial damage, as indicated by cTn, progresses during an exacerbated state of COPD has not been determined. Furthermore, the mechanisms that may contribute to elevations in cTn have not been established. We conducted a longitudinal study of cTn in patients with COPD and healthy individuals for 5 years. As our laboratory uses the T-isomere of cTn, we chose T-isomere of cTn as our outcome parameter.

The primary aim of the present study was to test the hypothesis that the cTnT level increases during incident severe AECOPD

compared with stable COPD. We also aimed to assess the effect of other hospitalisations on the cTnT level and to elucidate possible mechanism(s) for any increase in cTnT.

MATERIAL AND METHODS

Study population and design

The study was conducted at Akershus University Hospital and Glittre Rehabilitation Hospital. The population consisted of five cohorts: (1) candidates for long-term oxygen therapy (LTOT), (2) patients with COPD participating in the rehabilitation course at the hospital's outpatient clinic, (3) institutional COPD rehabilitation patients, (4) patients with COPD referred to the hospital's outpatient clinic and (5) a presumably healthy reference group.[17–19] All patients were in a stable state at inclusion, and none had AECOPD in the 6 weeks prior to inclusion. The reference group was selected by random sampling from the general population in the hospital's recruitment area. Seven of these 62 participants (11%) had irreversible airflow limitation, but none of them had their COPD diagnosed by a doctor.[17]

The LTOT candidates and the outpatient rehabilitation group were re-examined in the stable state 3 and 6 months after inclusion as a part of the routine programme, respectively. All participants were followed regarding acute hospitalisation until 5 years after inclusion. The main diagnosis at discharge was classified using the International Classification of Disease version 10. We included all diagnoses in order to compare changes in troponin between stable state and any cause of hospitalisation. All participants provided written consent.

Measurements

As our laboratory uses the T-isomere of cTn we chose T-isomere of cTn as our outcome parameter. High-sensitivity (hs)-cTnT at baseline was measured in venous serum samples stored at −80°C using a cobas e 411 immuno-analyser (Roche Diagnostics). The lower limit of detection was 3.0 ng/L. Using venous blood sampled at incident hospital admissions, hs-cTnT was analysed within 1 hour. Blood haemoglobin, blood leucocytes, serum C reactive protein (CRP) and serum creatinine were measured using routine laboratory methods. All of the blood samples were analysed at Akershus University Hospital's Clinical Biochemistry Laboratory.

At inclusion, spirometry was performed at the respiratory laboratories at Akershus University Hospital or Glittre Lung Rehabilitation Hospital as recommended by the European Respiratory Society/American Thoracic Society using the European Community for Coal and Steel reference equations.[20] A reversibility test was performed with 400 µg salbutamol unless the participant had inhaled a short-acting beta-2-stimulator or a short-acting muscarine receptor antagonist within 4 hours before spirometry.

Statistical analysis

Statistical analyses were performed in four levels. In the first level, we compared the baseline values of relevant variables in participants with incident hospitalisations to those of participants who were not hospitalised during the follow-up. Variables that were associated with hospitalisation with a corresponding $p<0.2$ were retained for further analysis in addition to established determinants of cTnT, such as gender, arterial oxygen tension and creatinine. Next, in the second level, we performed a multivariable linear regression analysis of the baseline data with hs-cTnT as the dependent variable using ordinary least square regression. In this analysis, we log-transformed hs-cTnT at inclusion (ln_ctnt0) because hs-cTnT was highly skewed to the right (online supplemental figure 1). Selected covariates were included using forward selection procedure. These covariates were added to the model, ordered by increasing numbers of missing values. In the final analysis of the baseline data, we invoked a model using multiple imputation.[21]

In the third level, we analysed the association between the level of hs-cTnT and the main diagnosis at each hospitalisation. The diagnoses were categorised into nine groups that were all inclusive and mutually exclusive. However, each participant could have several hospitalisations and different diagnoses during the follow-up. In these analyses, we invoked a multivariable model using log-transformed hs-cTnT (ln_ctnt) at follow-up as the outcome variable and diagnosis group at hospitalisation, baseline covariates (including baseline hs-cTnT) and routine clinical data during follow-up as the explanatory variables.

In the fourth level, we investigated whether the relationship between hs-cTnT and diagnosis was mediated in the longitudinal analyses by any of the following clinical variables at hospitalisation: blood leucocytes, serum CRP, arterial oxygen-tension, serum creatinine or heart rate. For details, see online supplemental figure 2. We performed these analyses using a multivariable mixed model with multiple imputations for missing values.[21] If the model did not converge, mixed model was replaced by ordinary least square regression with robust SEs. The time elapsed between inclusion and hospitalisation was also included as a covariate. Mediation of the relationship between diagnosis group and hs-cTnT by any of the clinical variables at follow-up was assessed in four steps: (1) The relationship between the potential mediator and diagnosis, adjusted for relevant covariates using a linear mixed model had to be significant (online supplemental equation 1). (2) The direct effect (θ1) of diagnosis group on ln_ctnt (θ1, online supplemental equation 2) using all relevant covariates, including clinical follow-up data, as explanatory variables had to be non-significant. (3) After removal of the clinical covariates or combinations of the clinical follow-up variables from this model we estimated the total effect of diagnosis group on ln_ctnt (T1, online supplemental equation 3). Finally (4), we estimated the natural indirect effect (ie, the mediation effect) of

Table 1 Baseline characteristics of the total cohort at inclusion

Characteristics	Total	Ever hosp.	Never hosp.	P value
Sex, female, n (%)	175 (46)	83 (44)	92 (48)	0.434
Age, years, mean (SD)	65.1 (7.6)	67.0 (6.9)	63.5 (7.9)	<0.001
Laboratory data, mean (SD)				
Haemoglobin, g/dL	14.2 (1.3)	14.1 (1.4)	14.2 (1.3)	0.423
Leucocyte count, 10^9/L	7.0 (2.2)	7.2 (2.4)	6.9 (2.0)	0.137
C reactive protein*, mg/L	2.6 (2.9)	3.0 (2.9)	2.2 (2.9)	0.006
Creatinine, mmol/L	75.5 (22.4)	76.6 (27.5)	74.5 (17.0)	0.352
hs-cTnT*, ng/L	6.9 (2.6)	8.8 (2.6)	5.6 (2.5)	<0.001
Clinical Variables, mean (SD)				
FVC, L	2.9 (1.3)	2.7 (1.4)	3.1 (1.1)	0.010
FEV1, L	1.6 (0.9)	1.4 (0.7)	1.8 (1.1)	<0.001
FVC of predicted, %	85.1 (28.1)	81.2 (34.1)	88.5 (21.4)	0.012
FEV1 of predicted, %	56.5 (27.4)	50.1 (24.0)	61.8 (29.0)	<0.001
Arterial O2-tension, kPa	9.3 (1.7)	9.2 (1.6)	9.4 (1.8)	0.335
Arterial CO2-tension, kPa	5.3 (0.8)	5.3 (0.8)	5.4 (0.8)	0.316
Systolic BP, mm Hg	134.1 (21.3)	134.6 (20.9)	133.6 (21.6)	0.670
Heart rate (ECG), 1/min	71.8 (12.9)	73.0 (13.6)	70.7 (12.1)	0.113
Q-wave ECG, n (%)	26 (8)	17 (11)	9 (6)	0.109
Clinical History, n (%)				
Coronary arterial disease	23 (6)	16 (9)	7 (3)	0.018
Arterial hypertension	155 (40)	78 (45)	77 (37)	0.134
Diabetes mellitus	24 (6)	13 (7)	11 (5)	0.389
Smoking habits				
Current smoking, n (%)	103 (27)	43 (25)	60 (29)	0.365
Former smoking, n (%)	244 (64)	125 (72)	119 (53)	0.003
Pack-years, mean (SD)	33.1 (21.0)	37.9 (20.3)	29.1 (20.8)	<0.001
Group				<0.001
References	63 (16)	12 (7)	51 (25)	
LTOT candidates	21 (5)	16 (9)	5 (2)	
Rehabilitation group				
Outpatients	63 (16)	47 (28)	16 (8)	
Institutional	63 (16)	13 (7)	50 (24)	
Unselected outpatients	173 (45)	87 (50)	86 (41)	

BP, Blood Pressure; CRP, C-Reactive Protein; FEV1, forced expiratory volume in 1 s; FEV1, Forced Expiratory Volume in one second; FVC, Forced Volume Capacity; Hosp, hospitalised; hs-cTnT, high-sensitivity cardiac troponin T; LTOT, long-term oxygen therapy.

diagnosis on hs-cTnT as the difference between T1 and θ1 (T1 – θ1). The SEs, and thereby the p values, of these differences were estimated using bootstrapping.[22] For details, see the online supplemental (mediation).

Continuous covariates were categorised in quartiles, and the analyses were performed using Stata V.16.1 (StataCorp).

RESULTS

Baseline analyses

Table 1 shows the baseline data for participants who were never hospitalised and those who were ever hospitalised during 5 years of follow-up. Totally, 30 and 23 patients were ever hospitalised for exacerbation or pneumonia, respectively. Among these patients, eight patients were hospitalised for exacerbation as well as pneumonia. We observed that individuals who were hospitalised during the follow-up were older, had higher baseline hs-cTnT, markedly lower spirometry results and higher cumulative tobacco consumption than those who were never

hospitalised. However, the prevalence of current smoking was not different between these two groups (table 1). Finally, the proportion of participants having incident hospitalisation during the follow-up was significantly different between the cohorts.

The univariable analyses of associations between hs-cTnT and covariates at baseline are shown in online supplemental table 1A,B. These analyses show that hs-cTnT was higher in males, patients with pathological Q-waves on the ECG, and participants with arterial hypertension than in their respective counterparts. However, hs-cTnT was lower in current smokers than current non-smokers. Similarly, the univariate ordinary least square regression analyses of hs-cTnT (expressed as ln_ctnt0) as the outcome and continuous covariate (in quartiles) showed a positive association with age, peripheral leucocyte count, CRP, creatinine and heart rate (online supplemental table 1B). Similarly, we identified a significant inverse relationship between hs-cTnT and spirometry variables, and with arterial oxygen tension.

Three participants were excluded from the analyses because they had missing values for forced expiratory volume in 1 s, blood leucocytes or smoking at baseline. Therefore, the analyses were restricted to the remaining 380 participants. All of these individuals had complete data regarding cohort group, gender, age, peripheral leucocytes, creatinine, spirometry, history of arterial hypertension, coronary heart disease and smoking status. The baseline data were incomplete regarding ECG (n=70), arterial oxygen tension (n=75) and serum CRP (n=27; online supplemental table 2).

The results of the multivariable analysis of the baseline data with ln_ctnt0 as the dependent variable by increasing the number of covariates without missing values as explanatory variables in ordinary least square regression are shown in table 2. After inclusion of pathological Q-wave as a covariate, the number of individuals available for analysis was reduced to 310 participants (82%). At this step, we observed that the hs-cTnT level was higher in the COPD groups than the reference group. After inclusion of the remaining continuous covariates, the number of participants available for analysis was reduced to 270 individuals (71% of the total sample). Interestingly, after these adjustments, hs-cTnT was not higher in any of the patient groups than the reference group. After application of multiple imputations, the SEs were generally smaller than in the full model without imputations. The coefficients were mainly unchanged but, without imputations, the programme failed to estimate the coefficient for the LTOT candidates.

Longitudinal analyses

The diagnoses, number of hospitalisations, number of hs-cTnT measurements and corresponding geometric mean and geometric SD (GSD) of hs-cTnT at baseline and hospitalisation by diagnosis group are summarised in table 3. The hs-cTnT measurements were available in 353 (74%) of hospitalisations. The fraction of hs-cTnT measurements was ≥85% in AECOPD, pneumonia, non-respiratory infections and diseases in the circulatory system. The overall geometric mean of hs-cTnT (corresponding GSD) at hospitalisation was 10.6 (2.5) ng/L (table 3). A detailed text version of the diagnoses is found in online supplemental table 3.

Analysis of the association between hs-cTnT and diagnosis at incident hospitalisations adjusted for follow-up time showed that hs-cTnT was significantly higher during the hospitalisation in AECOPD, pneumonia, 'other lung diseases', non-respiratory infections, circulatory diseases and 'other diagnoses' compared with the stable state (table 4, model 1). After adjusting for determinants of baseline hs-cTnT, the associations between hs-cTnT at follow-up and diagnoses was slightly attenuated for most

Table 2 Hs-cTnT measures at baseline and hospitalisation by diagnosis

				hs-cTnT: admittance		hs-cTnT: baseline		
Diagnosis at hospital admittance	N	n	n/N, %	GM	GSD	GM	GSD	Ratio
COPD exacerbation	150	140	93	19.7	2.1	12.6	2.4	1.6
Pneumonia	80	67	84	20.5	2.5	13.5	2.6	1.5
Other lung diseases	43	21	49	15.5	2.7	10.4	2.5	1.5
Non-respiratory infections	6	6	100	25.4	3.3	9.0	3.5	2.8
Circulatory diseases	52	48	92	15.5	2.7	9.5	1.9	1.6
Cancer	21	9	45	20.0	2.3	8.3	1.8	2.4
Digestive diseases	26	11	41	13.3	2.2	8.2	3.1	1.6
Symptom diagnoses	30	24	80	8.2	1.6	7.2	2.3	1.1
Other diagnoses	65	26	39	21.5	2.5	8.3	2.7	2.6
Total	473	352	74	10.6	2.5	7.1	2.6	1.5

Regarding ICD-10 diagnoses are given in online supplemental table 3.
COPD, chronic obstructive pulmonary disease ; GM, geometric mean; GSD, geometric SD; hs-cTnT, high-sensitivity cardiac troponin T; ICD-10, International Classification of Disease version 10.

Table 3 Ratio between the level of high-sensitive cardiac troponin T in four different models

	Model 1			Model 2			Model 3: total effects			Model 4: direct effects		
	Ratio	GSE	P value	Ratio	GSE	P value	Ratio	GSE	P value	Ratio	GSE	P value
Diagnosis												
AECOPD	1.47	1.10	<0.001	1.40	1.10	<0.001	1.27	1.11	0.023	1.08	1.12	0.513
Pneumonia	1.59	1.11	<0.001	1.53	1.11	<0.001	1.28	1.14	0.054	1.01	1.15	0.929
Other lung diseases	1.40	1.19	0.047	1.31	1.18	0.107	1.06	1.24	0.775	0.96	1.24	0.839
Non-respiratory infection	2.23	1.32	0.004	2.29	1.32	0.003	2.45	1.36	0.003	1.79	1.36	0.061
Circulatory diseases	2.78	1.14	<0.001	2.71	1.13	<0.001	2.12	1.18	<0.001	1.98	1.18	<0.001
Cancer	1.40	1.27	0.154	1.37	1.26	0.177	0.89	1.42	0.745	0.73	1.42	0.370
Digestive diseases	1.21	1.28	0.442	1.21	1.27	0.438	1.45	1.27	0.123	1.32	1.27	0.242
Symptom diagnoses	1.13	1.17	0.442	1.13	1.17	0.435	1.22	1.22	0.327	1.12	1.22	0.578
Other diagnoses	1.59	1.16	0.002	1.56	1.16	0.003	1.40	1.41	0.326	1.22	1.41	0.556
Follow-up time in years	1.13	1.03	<0.001	1.12	1.03	<0.001	1.11	1.04	0.004	1.12	1.04	0.004
Baseline covariates												
Study group vs references												
LTOT candidates				1.31	1.26	0.246	Omitted					
Institutional				0.96	1.19	0.836	Omitted					
Outpatients				0.82	1.18	0.232	0.81	1.11	0.039			
Outpatient clinic				0.53	1.21	0.001	Omitted					
Covariates. baseline												
Sex: female versus male				0.63	1.09	<0.001	1.00	1.09	0.978			
Age in quartiles				1.12	1.04	0.002	1.02	1.04	0.521			
Pack-years in quartiles				0.98	1.04	0.542	0.94	1.03	0.071			
Hypertension: Y vs N				1.24	1.08	0.009	0.94	1.08	0.420			
Coronary artery disease: Y vs N				1.10	1.18	0.576	1.19	1.29	0.491			
Q-wave ECG: Y vs N				1.04	1.16	0.783	1.01	1.14	0.962			
Continuous baseline covariates in quartile												
Creatinine				1.14	1.04	0.002	1.02	1.04	0.522			
Leucocytes				1.07	1.04	0.072	1.07	1.04	0.056			
C reactive protein				1.02	1.04	0.615	1.04	1.03	0.199			
FEV1				0.78	1.05	<0.001	0.99	1.04	0.729			
Arterial O_2-tension				0.89	1.05	0.018	0.94	1.04	0.114			
High-sensitive cardiac troponin T							1.93	1.04	<0.001	1.87	1.03	<0.001

Continued

Table 3 Continued

	Model 1			Model 2			Model 3: total effects			Model 4: direct effects		
	Ratio	GSE	P value	Ratio	GSE	P value	Ratio	GSE	P value	Ratio	GSE	P value
Biomarkers during follow-up in quartiles												
Leucocytes							1.09	1.04	0.015			
C reactive protein							1.08	1.04	0.038			
Creatinine							1.06	1.03	0.052			
Arterial O_2-tension							1.01	1.03	0.823			
Heart rate							1.08	1.03	0.028			

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; GSE, geometric SE; LTOT, long-term oxygen treatment.;

of the diagnosis group (table 4, model 2). When we included baseline hs-cTnT as a covariate, the relationships between diagnosis group and hs-cTnT, that is, the total effect, attenuated substantially more and was no longer significant regarding 'other diagnoses' (table 4, model 3). The relationship between hs-cTnT and AECOPD remained significant, but the association with pneumonia was not significant (p=0.054). Moreover, in model 3, the association between hs-cTnT at hospital admission and baseline covariates were no longer significant. Thus, baseline determinants of hs-cTnT were removed from the model, resulting in a more parsimonious model with fewer imputations (online supplemental table 5, full model).

In the next step, we added blood leucocytes, serum CRP, serum creatinine, arterial O2-tension and heart rate at hospital admission to the model. The association between all diagnoses, except circulatory diseases, and hs-cTnT (ie, the direct effect) at admission attenuated to zero (table 4, model 4). Furthermore, the relationships between hs-cTnT and leucocytes, CRP and heart rate, but not arterial O2-tension, at admission were significant. Therefore, we investigated the relationship between leucocytes, CRP and heart rate at admission as outcome variables and diagnoses, observation time, baseline hs-cTnT and covariates at hospitalisation as explanatory covariates in separate linear mixed models. A linear mixed model with heart rate as the outcome variable did not converge, even when we log-transformed heart rate. Therefore, in the analysis of heart rate, we replaced the linear mixed model with ordinary least square regression and robust SEs. In these analyses, both leucocytes and CRP were positively related to AECOPD, pneumonia, non-respiratory infections and circulatory diseases, whereas the association between heart rate and diagnoses was not significant (online supplemental table 4).

Finally, we estimated the indirect effect of AECOPD, pneumonia and non-respiratory infection on hs-cTnT as the difference between the total effect and the direct effect: IE=T1 − θ1. SEs were obtained by bootstrapping the difference using 100 replications (online supplemental table 5). Leucocytes and CRP jointly had a significant effect on the ratio between hs-cTnT at hospital admission and hs-cTnT in the stable state, that is, mediated the effect of AECOPD, pneumonia and non-respiratory infections on hs-cTnT. It is likely that this joint effect of CRP and leucocytes is indirect, that is, mediated by some factor(s) that we did not have information about. The joint effects of leucocytes and CRP on the indirect effect of AECOPD and pneumonia on hs-cTnT represented 91% (95% CI 82% to 100%) and 95% (95% CI 83% to 100%) of the total effects, respectively. The corresponding results for non-respiratory infections was 51% (95% CI 36% to 74%). As leucocytes were highly significantly related to circulatory diseases, we also estimated the indirect effect of leucocytes by circulatory diseases. This indirect effect was not significant (p=0.125).

Table 4 The natural indirect effect of AECOPD, pneumonia and non-respiratory infections on the ratio of high-sensitivity cardiac troponin T at admission versus stable state with corresponding GSE and p values mediated by peripheral leucocytes and CRP per quartile

	AECOPD			Pneumonia			Non-respiratory infections		
	Ratio	GSE	P value	Ratio	GSE	P value	Ratio	GSE	P value
Leucocytes	1.07	1.04	0.082	1.06	1.04	0.183	1.13	1.07	0.053
CRP	1.05	1.03	0.096	1.11	1.06	0.080	1.07	1.04	0.061
Leucocytes or CRP	1.16	1.07	0.022	1.22	1.08	0.008	1.26	1.12	0.043

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP, C reactive protein; GSE, geometric SE.

Discussion

In this study, we found that AECOPD and pneumonia may elevate cTnT indirectly by increasing systemic inflammation. We also found the same effect for non-respiratory infections.

To the best of our knowledge, a positive association between indices of systemic inflammation that is induced by AECOPD or pneumonia, that is, airways inflammation, and myocardial injury has not been described before.

The main strength of this study is that patients were enrolled in stable state, and that diagnoses at hospital admission were made without any knowledge about their state at inclusion. Moreover, in the majority of the patients hospitalised for exacerbation and pneumonia measurements of troponin was available.

Because the association between AECOPD and pneumonia with hs-cTnT attenuated substantially after inclusion of leucocytes and CRP as covariates, one may wonder whether leucocytes and CRP should be regarded as confounders of the relationship between AECOPD and cTnT. However, we think a causal relationship exists between AECOPD and the increase in leucocytes and CRP. Therefore, leucocytes and CRP should be regarded as mediators, not as confounders, of the relationship between AECOPD and troponin elevation.[23 24] We think these considerations also encompass pneumonia insofar as the total effect of pneumonia on cTnT elevation was the same as that of AECOPD. The p value for pneumonia was lower than the p value for AECOPD mostly because of fewer pneumonia events relative to AECOPD. Moreover, the distinction between pneumonia and AECOPD in patients with COPD is not clear.

As the increase in leucocytes in AECOPD and pneumonia reflects an effect of airway inflammation on the bone marrow, and the increase in CRP is caused by cytokines produced by circulating granulocytes, we regard the joint effect of leucocytes and CRP in these events as a systemic effect of AECOPD and pneumonia. Furthermore, systemic inflammation may increase cTn, particularly in severe infections.[25] This is in agreement with our findings regarding non-respiratory infections. On the other hand, circulatory diseases were weakly associated with leucocytes and CRP, and the cTnT level in this group was nearly unchanged after inclusion of leucocytes and CRP as covariates. Thus, the cTnT elevation was likely a direct consequence of myocardial disease.

The clinical implication of our finding is that reduction of systemic inflammation be given more focus in the treatment of COPD.

Heart rate was also positively associated with troponin elevation, but not with AECOPD or pneumonia, and removal did not change the relationship between AECOPD or pneumonia and troponin. Thus, the confounding effect of heart rate was negligible and it was not a mediator the relationship between AECOPD or pneumonia and troponin.

We also noted that we did not find any association between troponin and hypoxaemia. This is in agreement with two other previous cohorts.[26 27] As in our previous studies, we did not have information on oxygen tension in the patients prior to admission. Moreover, it could also be explained by insufficient number of patient. Therefore, we cannot exclude hypoxaemia as a putative contributor of troponin elevation at admission.

Several studies have reported that troponin elevation is associated with the severity of stable COPD and that troponin elevation is associated with an unfavourable prognosis after COPD exacerbation and in the stable state.[28] The relationship between AECOPD and increased troponin has been less studied. In a cohort of 98 stable patients with COPD who were followed over several months, 55 patients were investigated in both their stable state and during exacerbation.[29] Among these patients, 24 who had verified an infectious cause of the exacerbation had troponin elevation during the exacerbation. This elevation was most pronounced in patients with concomitant coronary artery disease. In another study, a minority of patients referred to hospital due to AECOPD had elevated cTnT that normalised within 72 hours of admission.[30] However, in the latter study, they had not determined cTnT values in the stable state prior to hospitalisation. Therefore, they could not adjust for cTnT in the stable state prior to admission.

The main limitation of this study was that we did not re-examine the individuals who were not hospitalised during the follow-up, except the LTOT candidates and members of the outpatient rehabilitation group. Therefore, data about the natural course of cTnT in the cohort were sparse. However, this limitation should not distort the results, as we adjusted for follow-up time in the analyses.

In conclusion, systemic inflammation in COPD caused by exacerbation or pneumonia mediates elevation of cTnT.

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Contributors VS: design, data managment, analyses, main author; NK: data collection, manuscript preparation; AN: data collection, manuscript preparation; NHH: data collection, manuscript preparation; T-AH: laboratory services, manuscript preparation; TO: design manuscript preparation; GE: design, manuscript preparation.

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Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request.

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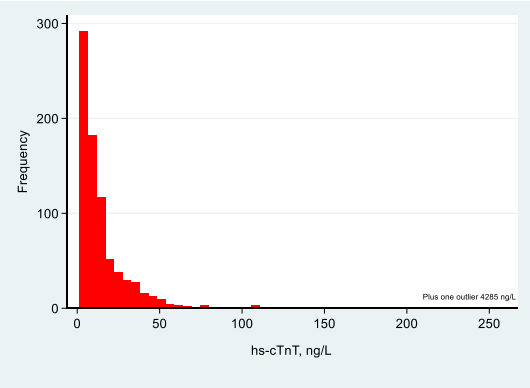
Online figure 1. Distribution of high-sensitivity Troponin T (hs-cTnT).



(The outlier had acute myocardial infarction).

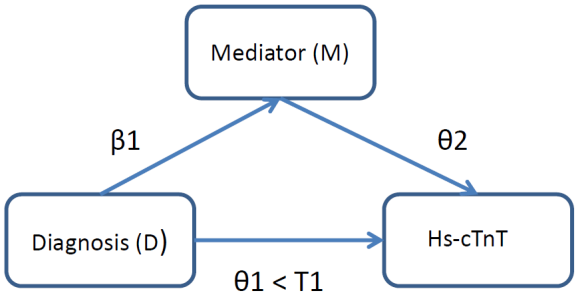
Mediation, prerequisites:

In our settings, the variable (M) was considered as a mediator of the relationship between the disease (D) and hs-cTnT provided that:

1. M was significantly associated with D (β1, Equation 1).
2. In a model with hs-cTnT as the outcome using D and M as explanatory variables, M was significantly associated with hs-cTnT (θ_2, Equation 2).
3. In a model without M, D was significantly associated with hs-cTnT (T1, Equation 3).
4. In a model with M and D, the association between D and the hs-cTnT attenuated substantially (θ1, Equation 2).

In these analyses, we first investigated the association between M and D between M and relevant covariates (c), (eq 1). In these analyses, CRP as well as leucocytes were log-transformed. Thereby, we estimated the coefficients (β1) between M and D. Second, we investigated the relationship between the outcome variable expressed as log-transformed hs-cTnT (ln_ctnt), using D, M and relevant covariates (c) as explanatory covariates (eq 2). Thereby, we estimated the relationship between ln_ctnt and D (θ1). Third, we removed M from eq 2 and estimated the relationship between ln_ctnt and D (T1) unconditionally of M but kept the covariates (c. Finally, the indirect association between ln_ctnt was calculated as the difference between β1 and β0 (eq 3: IE = β1 – β0). The corresponding z-score (and p-values) were obtained using bootstrapping.

Online figure 2.



- Eq 1:
  $E(M \mid D, c1) = \beta_0 + \beta_1 * D + \beta_{11} * c1$
- Eq 2:
  $E(ln\_ctnt \mid D, M, c2) = \theta_0 + \theta_1 * D + \theta_2 * M + \beta_{22} * c2$
- Eq 3:
  $E(ln\_ctnt \mid D, c2) = T_0 + T_1 * D + \beta_{32} * c2$

- Direct effect: $\theta 1$
- Indirect effect: IE = T1 - $\theta 1$
- Total effect: T1
- c1, c2: other covariates in eq 1, eq 2 and 3, respectively.

The relationship between ln_ctnt as the outcome variable and diagnoses with biomarkers as well as baseline hs-cTnT and follow-up time as covariates were estimated using linear mixed model (four models). In these analyses we used multiple imputations for C-reactive protein, oxygen tension, and creatinine (we had complete data for leucocytes, see online table 2). Standard errors for IE, and thereby the corresponding p-values, were obtained using bootstrapping. The continuous covariates were included in quartiles.

Online table 1a. The geometric mean of high sensitivity cardiac Troponin T (hs-cTnT), the ratio of hs-cTnT between index-group (Yes) and reference group (No) with geometric standard error (gse) and p-value by categorical covariables and study group at baseline (n = 380).

Explanatory variables	Hs-cTnT, ng/L		
	Yes	No	Ratio (gse, p-value)
Female gender: Yes vs. No	5.4	8.7	0.62 (1.1, <0.001)
Coronary heart disease: Yes vs. No	8.8	6.8	1.3 (1.2, 0.207)
q-wave in electrocardiogram: Yes vs. No	10.5	6.8	1.5 (1.2, 0.034)
Arterial hypertension: Yes vs. No	8.5	5.9	1.4 (1.1, <0.001)
Current smoking: Yes vs. No	5.9	7.4	0.79 (1.2, 0.024)

Online table 1b. The geometric mean of high sensitivity cardiac Troponin T (hs-cTnT) and the ratio of hs-cTnT (Ratio = hs-cTnT$_{Qn+1}$/ hs-cTnT$_{Qn}$) between quartiles (Q1-4) of hs-cTnT with geometric standard error (gse), by continuous covariates in quartiles measured at baseline (n = 380).

Variables (quartile limits)	Q1	Q2	Q3	Q4	Ratio§	gse	p-value
Age, years (60.0; 65.0; 70.0)	4.7	6.3	7.2	10.6	1.3	1.04	<0.001
Leucocytes, x10^9/litres (5.7; 6.8; 8.1)	5.8	6.2	7.3	8.6	1.1	1.05	0.002
CRP, mg/litres (1.0; 3.0; 4.0)	6.3	6.2	6.7	8.5	1.1	1.04	0.031
Creatinine, mmol/litres (63.0; 72.0; 84.0)	6.1	5.5	7.0	9.5	1.2	1.04	<0.001
FEV1, litres (0.9; 1.3; 2.0)	10.2	6.8	5.4	5.8	0.82	1.04	<0.001
FVC , litres (2.1; 2.7; 3.5)	8.4	6.9	6.4	5.9	0.89	1.05	0.011
Arterial O2-tension, kPa (8.4; 9.2; 10.2)	10.0	7.1	6.4	6.3	0.86	1.05	0.003
Heart Rate, 1/minutes (63; 72; 80)	6.0	6.0	6.9	10.0	1.2	1.05	0.001
Tobacco, pack-years (0.4; 26.4; 45.0)	6.1	6.8	7.1	7.7	2.1	1.04	0.086

§ Ratio = Q_n/Q_{n-1}

Online Table 1c. Baseline ratio of high-sensitivity troponin T and different levels of relevant covariates in three models using ordinary least square regression with missing values and a model using multiple imputations for missing values.

	Ordinary Least Square Regression without imputation									Multiple Imputation		
Observations (N)	N = 380			N = 310			N = 270			N = 380		
Group	Ratio	GSE	p-value	Ratio	GSE	p-value	Ratio	GSE	p-value	Ratio	GSE	p-value
References	1.00	-	-	1.00	-	-	1.00	-	-	1.00	-	-
LTOT candidates	2.82	1.25	<0.001	2.25	1.28	0.001	Omitted			1.43	1.41	0.295
Rehabilitation group												
Outpatients	1.33	1.17	0.065	1.24	1.18	0.193	0.67	1.29	0.118	1.08	1.36	0.794
Institutional	1.36	1.14	0.017	1.46	1.15	0.007	0.67	1.26	0.086	1.03	1.34	0.930
COPD outpatients	1.09	1.17	0.578	Omitted			0.39	1.27	<0.001	0.60	1.36	0.102
Sex: female vs. male	0.60	1.09	<0.001	0.63	1.11	<0.001	0.60	1.13	<0.001	0.59	1.11	<0.001
Age in quartiles	1.25	1.04	<0.001	1.22	1.05	<0.001	1.12	1.05	0.035	1.16	1.04	<0.001
Pack-years in quartiles				0.95	1.05	0.302	1.01	1.05	0.901	0.97	1.04	0.488
Arterial hypertension: Y vs. N				1.30	1.11	0.013	1.25	1.11	0.040	1.24	1.10	0.018
Coronary arterial disease: Y vs. N				1.25	1.25	0.302	1.06	1.25	0.793	1.03	1.21	0.880
Q-wave ECG: Y vs. N				1.22	1.20	0.286	1.18	1.20	0.352	1.17	1.17	0.317
Heart rate in quartiles				1.19	1.05	<0.001	1.07	1.05	0.201	1.09	1.04	0.040
Continuous covariates in quartiles												
Creatinine							1.12	1.06	0.032	1.14	1.05	0.006
C-reactive protein							1.00	1.05	0.920	1.02	1.04	0.657
Peripheral leucocytes							1.04	1.05	0.387	1.05	1.04	0.224
FEV1							0.76	1.06	<0.001	0.76	1.05	<0.001
Arterial O2-tension							0.93	1.06	0.197	0.93	1.05	0.116

GSE: geometric standard error, LTOT: long-term oxygen treatment, COPD: chronic obstructive pulmonary disease, ECG: electrocardiogram, FEV1: forced expiratory volume in 1 second.

Online table 2. The number of complete data, the percent of imputed numbers and the total number by baseline model and longitudinal models.

Variable, quartiles	Complete	Imputed, %	Total
Baseline model			
Arterial O_2-tension	305	20	380
Heart rate	310	18	380
Q-wave ECG	310	18	380
C-Reactive Protein	353	7	380
Longitudinal models			
Arterial O_2-tension	770	4	801
C-Reactive Protein	800	0	801
Creatinine	667	17	801
Leucocytes	801	0	801
Heart rate	786	2	801

Online table 3. International Classification of Disease code (ICD10), text explanation, the number of hs-cTnT measurements at baseline (N) and during the follow-up (n), and the corresponding geometric mean (gm) and geometric standard deviation (gsd) of high-specific Cardiac Troponin by Diagnoses at the follow-up.

ICD10	Diagnosis, text	N	n	n/N, %	Baseline		Hospitalised	
					gm	gsd	gm	gsd
Acute Exacerbation of COPD								
J44.0	COPD with acute infection in the lower respiratory airways	19	17	89	15.2	1.9	34.9	2.1
J44.1	Unspecified acute exacerbation of COPD	130	122	94	12.2	2.5	18.2	2.1
J96.0	Acute Respiratory Failure	1	1	100	14.4		21.0	
	Sum	150	140	93	12.6	2.4	19.7	2.1
Pneumonia								
J13	Pneumonia due to P.pneumonia	5	4	80	12.2	4.2	17.8	1.8
J14	Pneumonia due to H.Influenzae	1	1	100	13.0		14.0	
J15	Bacterial Pneumonia, not elsewhere classified	22	17	77	14.2	2.1	31.3	2.4
J18	Pneumonia, unspecified organism	52	45	87	13.3	2.7	17.8	2.6
	Sum	80	67	84	13.5	2.6	20.5	2.5
Other Lung diseases								

J09	Influenza due to certain identified viruses	1	1	100	12.9		29.0	
J10	Influenza due to other identified viruses	3	3	100	11.4	2.2	43.7	2.9
J12	Viral pneumonia	3	3	100	5.7	1.3	4.7	2.7
J20	Acute bronchitis	3	2	67	9.7	1.4	28.4	1.1
J22	Unspecified lower respiratory infection	1	0	0	7.1			
J33	Nasal polyp	1	0	0	14.0			
J43	Emphysema	2	1	50	15.8	2.8	15.0	
J44	Other chronic obstructive disease	8	4	50	19.8	3.0	23.8	1.7
J47	Bronchiectasis	1	0	0	10.0			
J84	Other interstitial pulmonary diseases	1	0	0	3.9			
J85	Abscess of lung or mediastinum	2	0	0	38.9	1.3		
J90	Pleural effusion, not elsewhere classified	1	0	0	31.2			
J93	Pneumothorax	5	2	40	6.5	2.4	13.6	4.1
J96	Respiratory failure, not elsewhere classified	11	5	45	6.8	2.2	8.8	1.7
	Sum	43	21	49	10.4	2.5	15.5	2.7
Non-respiratory infections								
A04	Other intestinal infections	1	1	100	6.0		13.5	
A09	Other gastroenteritis and colitis, unspecified agent	3	3	100	5.3	4.3	13.5	2.6
A46	Erysipelas	1	1	100	13.0		15.0	
A49	Bacterial infection, unspecified	1	1	100	45.9		162.0	
	Sum	6	6	100	9.0	3.5	25.4	3.3
Diseases of the circulatory system								
I11	Hypertensive heart disease	1	1	100	11.0		22.0	
I20	Angina pectoris	12	12	100	11.3	1.3	14.6	2.5
I21	Acute myocardial infarction	7	7	100	7.4	2.1	161.5	6.2
I24	Other acute ischaemic heart disease	1	1	100	11.0		11.0	
I25	Chronic ischaemic heart disease	8	7	88	10.6	1.7	15.9	2.8
I26	Pulmonary embolism	2	2	100	12.6	1.4	14.5	1.0
I42	Acute myocarditis	2	2	100	8.7	1.5	78.2	1.5
I46	Cardiac arrest	1	1	100	2.1		6.2	
I48	Atrial fibrillation and flutter	6	6	100	4.6	3.0	28.2	2.1
I50	Heart failure	3	2	67	18.4	2.2	15.5	1.0
I60	Subarachnoid haemorrhage	1	1	100	14.0		262.0	

I61	Intracerebral haemorrhage	2	2	100	4.7	1.5	7.1	1.6
I63	Cerebral infarction	3	3	100	13.6	2.5	7.1	4.9
I67	Other cerebrovascular disease	1	1	100	14.0			
I71	Aortic aneurysm and dissection	1	0	0	9.3			
I81	Phlebitis and thrombophlebitis	1	0	0	12.6			
	Sum	52	48	92	9.5	1.9	26.8	3.9
Cancer								
C21	Malignant neoplasm of anus and anal canal	1	0	0	3.0		32.0	
C25	Malignant neoplasm of pancreas	2	1	50	10.8	3.4	32.0	
C34	Malignant neoplasm of bronchus and lung	8	3	38	7.7	1.6	38.7	2.0
C50	Malignant neoplasm of the breast	1	0	0	4.6			
C61	Malignant neoplasm of prostate	1	1	100	12.9		17.0	
C64	Malignant neoplasm of the kidney, except renal pelvis	2	1	50	13.6	3.2	38.0	
C67	Malignant neoplasm of the bladder	3	1	33	8.2		15.0	
C72	Malignant neoplasm of the spinal cord, cranial nerves and others	1	0	0	5.9			
C78	Secondary malignant neoplasm of respiratory and digestive sites	1	1	100	14.4		16.0	
C90	Multiple myeloma	1	1	100	8.9		5.0	
	Sum	21	9	43	8.3	1.9	22.4	2.2
Diseases of the digestive system								
K21	Gastro-oesophageal reflux disease	2	1	50	3.4	1.2	5.0	
K29	Gastritis and duodenitis	4	4	100	14.3	8.4	17.7	2.9
K35	Acute appendicitis	1	0	0	45.5			
K42	Umbilical hernia	1	0	0	14.0			
K44	Diaphragmatic hernia	1	1	100	4.5			
K52	Other noninfective gastroenteritis and colitis	1	0	0	11.0			
K56	Paralytic ileus and intestinal obstruction without hernia	3	0	0	2.6	2.6		
K57	Diverticular disease	4	1	25	9.3	2.6	27.0	
K61	Abscess of anal and rectal regions	1	0	0	1.5			
K62	Other diseases of anus and rectum	1	0	0	12.0			
K63	Other diseases of intestine	1	0	0	19.0			
K72	Hepatic failure, not elsewhere classified	4	2	50	11.0	2.5	9.5	2.5
K82	Other diseases of the gall bladder	1	0	0	10.5		1.0	
K92	Other diseases of the digestive system	1	1	100	7.3		14.0	

	Sum	26	10	38	8.3	3.1	13.3	2.3
Symptoms								
R06	Abnormalities of breathing	1	0	0	1.5			
R07	Pain in chest and throat	17	17	100	8.3	1.9	8.3	1.6
R10	Abdominal and pelvic pain	4	2	50	11.8	2.9	8.9	2.3
R11	Nausea and vomiting	1	1	100	1.5		5.0	
R19	Other symptoms and signs involving the digestive system and bad.	1	1	100	8.5		8.0	
R33	Retention of urine	1	0	0	7.7			
R33	Retention of urine	2	0	0	11.9	1.1		
R42	Dizziness and giddiness	1	1	100	8.5		5.0	
R55	Syncope and collapse	2	2	100	2.1	1.6	11.2	2.4
	Sum	30	24	80	7.2	2.3	8.2	1.6
Other diagnoses								
D1	Benign neoplasms of mouth and pharynx	2	0	0	10.4	1.1		
D3	Benign neoplasm of specified organs	1	0	0	3.0			
D4	Benign neoplasm of uncertain origin	1	0	0	10.0			
D6	Aplastic anaemia	2	1	50	22.8	2.7	34.0	
D7	Other diseases of blood and blood-forming organs	1	0	0	14.0			
E0	Disease of the thyroid gland	1	0	0	5.3			
E1	Diabetes mellitus	2	2	100	15.5	2.7	19.6	2.7
E8	Metabolic disease, unspecified	3	3	100	26.3	1.5	17.0	2.9
F0	Organic mental disorder	2	2	100	32.5	1.0	28.1	1.3
F4	Neurotic disorder	1	1	100	11.0		11.0	
G4	Episodic paroxysmal disorder	4	2	50	6.8	2.6	19.9	3.1
M1	Inflammatory polyarthropathies or arthrosis	4	0	0	6.4	2.1		
M4	Dorsopathies, specified	2	0	0	3.0	1.0		
M5	Dorsopathies, unspecified	3	1	33	1.9	1.5	4.0	
M7	Other tissue disorders	1	1	100	12.9			
N1	Renal tubulo-interstitial diseases	2	2	100	22.5	2.7	73.9	2.5
N3	Other diseases of urinary system	3	2	67	10.9	1.3	12.0	1.1
N8	Noninflammatory disorders of female genital tract	1	0	0	1.5			
Q4	Other congenital malformations of upper alimentary tract	1	0	0	10.4			
S0	Injuries to the head	3	2	67	13.8	12.8	24.6	9.5

S2	Injuries to the thorax	2	0	0	11.2	1.0		
S3	Injuries to the abdomen, lower back, lumbar spine or pelvis	1	0	0	8.0			
S4	Injuries to the shoulder or upper arm	2	0	0	3.4	1.0		
S5	Injuries to the elbow and forearm	1	0	0	3.5			
S6	Injuries to the wrist and hand	1	0	0	1.5			
S7	Injuries to the hip and thigh	6	2	33	14.0	1.7	54.1	2.4
S8	Injuries to the knee or lower leg	1	0	0	1.5			
T4	Poisoning to narcotics and psychodysleptics	4	3	75	6.4	1.7	17.3	1.3
T8	Complication to medical treatment	3	1	33	6.2	3.4	36.0	
Z0	Health investigation	1	1	100	11.0		11.0	
Z4	Persons encountering health services for specific procedures	1	0	0	11.5			
Z5	Persons with health hazards related to socioeconomic circumstances	1	0	0	4.5			
Z9	Persons encountering health services in other circumstances	1	0	0	7.8			
	Sum	65	26	40	8.3	2.7	21.5	2.5

Online table 4. The ratio, geometric standard error (gse) and p-value between leucocytes counts, C-reactive protein, and heart rate, respectively, at hospitalization and stable state by relevant covariates.

	Leucocytes			C-reactive protein			Heart rate		
Diagnosis Group	Ratio	gse	p-value	Ratio	gse	p-value	Ratio	gse	p-value
COPD exacerbation	1.35	1.07	<0.001	4.37	1.25	<0.001	0.99	1.03	0.795
Pneumonia	1.25	1.09	0.012	18.28	1.31	<0.001	0.99	1.03	0.732
Other lung diseases	1.27	1.15	0.086	2.77	1.55	0.020	1.08	1.06	0.165
Non-respiratory infections	1.73	1.22	0.005	9.35	1.87	<0.001	0.93	1.04	0.043
Circulatory diseases	1.28	1.11	0.017	1.55	1.41	0.200	1.03	1.03	0.381
Cancer	1.64	1.25	0.026	2.29	2.04	0.244	0.97	1.08	0.692
Digestive diseases	1.16	1.16	0.320	1.18	1.62	0.738	1.06	1.06	0.258
Symptoms	1.39	1.13	0.009	1.83	1.51	0.142	1.04	1.03	0.297
Other diagnoses	1.37	1.25	0.154	2.03	2.01	0.309	1.01	1.04	0.872
Follow-up time: years	1.01	1.02	0.770	1.00	1.08	0.962	0.97	1.01	<0.001
Continuous covariates: quartiles									
Hs-cTnT at stable state	1.00	1.02	0.790	1.02	1.06	0.740	1.04	1.01	<0.001
Peripheral leucocytes	n.i.			1.38	1.08	<0.001	1.04	1.01	<0.001
C-Reactive protein	1.04	1.02	0.063	n.i.			1.01	1.01	0.324
Creatinine	1.01	1.02	0.450	0.98	1.07	0.798	0.97	1.01	<0.001
Arterial O2-tension	1.00	1.02	0.851	0.85	1.07	0.014	0.98	1.01	0.017
Heart rate	1.08	1.02	<0.001	0.99	1.07	0.928	n.i.		

n.i.: not included

Online table 5. Ratio (R) with geometric standard error (gse) and p-value (p) between the level of high-sensitive Troponin T (hs-cTnT) at hospitalisation and stable state by diagnosis, study group, hs-cTnT at baseline and covariates at hospitalisation in five different models.

	Full Model			Leucocytes removed			CRP removed			Heart Rate removed			Leuc. + CRP removed		
	R	gse	p	R	gse	p	R	gse	p	R	gse	p	R	gse	p
AECOPD	1.08	1.12	0.513	1.16	1.12	0.182	1.14	1.12	0.243	1.06	1.12	0.602	1.25	1.11	0.036
Pneumonia	1.01	1.15	0.929	1.08	1.15	0.609	1.14	1.14	0.318	1.00	1.15	0.989	1.25	1.14	0.084
Other Lung Dis.	0.96	1.24	0.839	1.01	1.24	0.953	1.01	1.24	0.975	0.96	1.25	0.865	1.09	1.24	0.708
Non-Resp. Infections	1.79	1.36	0.061	2.03	1.36	0.022	1.94	1.36	0.032	1.73	1.36	0.079	2.28	1.36	0.007
Circulatory Diseases	1.98	1.18	<0.001	2.12	1.18	<0.001	1.97	1.18	<0.001	1.94	1.18	<0.001	2.13	1.18	<0.001
Cancer	0.73	1.42	0.370	0.82	1.42	0.564	0.75	1.42	0.405	0.72	1.42	0.345	0.85	1.42	0.650
Digestive Diseases	1.32	1.27	0.242	1.35	1.27	0.215	1.31	1.27	0.255	1.34	1.27	0.226	1.34	1.27	0.224
Symptom Diagnoses	1.12	1.22	0.578	1.14	1.22	0.506	1.11	1.22	0.595	1.10	1.22	0.636	1.14	1.22	0.515
Remaining Diagn.	1.22	1.41	0.556	1.29	1.41	0.459	1.23	1.41	0.548	1.22	1.41	0.557	1.31	1.41	0.437
Follow-up time. Yrs.	1.12	1.04	0.004	1.13	1.04	0.002	1.12	1.04	0.004	1.11	1.04	0.006	1.13	1.04	0.002
Continuous Covariates in quartiles															
hs-cTnT baseline	1.87	1.03	<0.001	1.87	1.03	<0.001	1.88	1.03	<0.001	1.89	1.03	<0.001	1.87	1.03	<0.001
Continuous Covariates at admission in quartiles															
Leucocytes	1.09	1.04	0.015	removed			1.10	1.04	0.005	1.11	1.04	0.003	removed		
CRP	1.08	1.04	0.038	1.09	1.04	0.015	removed			1.08	1.04	0.034	removed		
Creatinine	1.06	1.03	0.052	1.07	1.03	0.034	1.06	1.03	0.058	1.05	1.03	0.111	1.07	1.03	0.036
Arterial O2	1.01	1.03	0.823	1.01	1.03	0.845	1.00	1.03	0.995	1.00	1.03	0.954	1.00	1.03	0.948
Heart rate	1.08	1.03	0.028	1.09	1.03	0.005	1.08	1.03	0.024	removed			1.10	1.03	0.003

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