It is unlikely that oxygen supplementation in COPD patients with chronic respiratory failure reduce cardiac troponin level

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Abstract

Background Cardiac troponin T (cTnT) is a biomarker of myocardial injury frequently elevated in COPD patients, potentially because of hypoxemia. This non-randomised observational study investigates whether long-term oxygen treatment (LTOT) reduces the cTnT level.

Methods We compared cTnT between COPD patients who were candidates for LTOT (n = 20) with two reference groups. Patients from both reference groups were matched with the index group using propensity score. Reference groups consists of institutional pulmonary rehabilitation patients (short-term group) (n = 105 after matching n = 11) and outpatients at a pulmonary rehabilitation clinic (long-term group)(n = 62 after matching n = 10). Comparison was done within 24 h after LTOT initiation in first reference group and within 6 months after inclusion in the second group.

Results The geometric mean of (standard deviation in parentheses) cTnT decreased from 17.8 (2.3) ng/L (between 8 and 9 a.m.) to 15.4 (2.5) ng/L between 1 and 2 p.m. in the LTOT group, and from 18.4 (4.8) ng/L to 15.4 (2.5) ng/L in group (1) The corresponding long-term results were 17.0 (2.9) ng/L at inclusion (between 10 and 12 a.m.) to 18.4 (2.4) ng/L after 3 months in the LTOT-group, and from 14.0 (2.4) ng/L to 15.4 (2.5) ng/L after 6 months in group (2) None of the differences in cTnT during the follow-up between the LTOT-group and their matched references were significant.

Conclusion Initiation of LTOT was not associated with an early or sustained reduction in cTnT after treatment with oxygen supplementation.
Background
Cardiac troponins T (cTnT) and I (cTnI) in peripheral circulation are highly specific and sensitive biomarkers of myocardial cell damage. The troponin complex is composed of three proteins: troponin T, troponin I, troponin C (TnT, TnI and TnC). It is located on the thin filament of the contractile apparatus in all types of striated (skeletal and cardiac) muscle, but is not found in the smooth muscle [1].

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by irreversible airflow limitation and associated with an enhanced inflammatory response to noxious particles or gases in the airways and the lung [2]. One important and dangerous complication of COPD is chronic respiratory failure. This is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination of the blood. Prognosis is quite poor and Long-Term Oxygen Treatment (LTOT) is a recommended treatment to improve survival and quality of life of hypoxemic COPD patients [2].

Previous retrospective and prospective studies have shown elevations of cardiac troponin during COPD exacerbations[3, 4] and in a stable disease [5]. cTnT in COPD patients is associated with increased mortality, independently of presence of cardiac disease[3, 5–7].

However, the underlying pathophysiological mechanisms of cardiac troponin (cTn) release in COPD are still incompletely understood. Possible mechanisms include physiological stressors such as tachycardia and hypoxemia leading to subclinical ischemic injury and leakage of cTn to the circulation.

We hypothesized that treatment of hypoxemia by supplementary oxygen may oppose and reduce ischemic injury, and thereby reduce cTn in the circulation.

Therefore, in the present study we aimed to test this hypothesis by assessing the short-term and long-term effects initiating of LTOT on circulatory cTnT concentration in stable COPD patients with chronic respiratory failure.

Materials and methods
Study population and design
This is a “non-randomised study” of the effect of oxygen supplementation on cTnT in COPD patients with respiratory failure. Inclusion criteria were diagnosed COPD (forced expiratory volume in one second (FEV₁) / forced vital capacity (FVC)<70% after inhalation of 400 µg salbutamol), age above 40 years and a cumulative tobacco consumption of 10 pack-years or more. For the intervention group, the following clinical criteria for initiation of LTOT were used:
1. Resting partial pressure of arterial oxygen [PaO₂] of <7.3 kPa (55 mmHg).
2. PaO2 < 8.0 kPa (60 mm Hg) in case of concomitant signs of right-sided heart failure, pulmonary hypertension or secondary polycythemia.
3. Non-smokers for at least three months, adjudicated by the attending physician.

Exclusion criteria for the study were: history of asthma or other lung diseases, current exacerbation of COPD and absence of competence to provide writing consent to participation.

A consecutive set of 23 COPD patients electively admitted to the Pulmonary Department, Akershus University Hospital, Norway, were considered for eligibility for the intervention group. A total of 3 patients were not accepted for LTOT: one patient developed CO₂-retension, one patient had used tobacco<3 months and one suffered from a current COPD exacerbation. The remaining 20 patients were included in the intervention group in the present study (Fig. 1). Among these 18 patients followed-up at three months after inclusion.

The LTOT candidates followed the clinical routine with a 24 h hospitalisation during initiation of LTOT to test their tolerance for oxygen. They were readmitted after 3 months for reassessment of oxygen dose. An ambulatory team (pulmonary nurse and physiotherapist) visited the patients between these two hospitalizations to facilitate the use of LTOT.

The observational references were enrolled from an institutional COPD rehabilitation program at LHL-hospi
tal Glittre (In-patients references) (n=118), and from an outpatient COPD rehabilitation program at Akershus University Hospital (out-patients references) (n=63). Thirteen patients were excluded from the in-patients reference group: 10 patients were LTOT-users, and six (three of them were LTOT-users) patients did not have measurement of cTnT at all the three time points (see data collection). The out-patients references were reas
essed 6 months after inclusion as a part of their rehabilita
tion program. In this group one patient was excluded due to LTOT (Fig. 1).

The flowchart shows the patients who started LTOT and gave their consent for participation in the study (n=20), their matched short-term references (n=11), and the matched long-term references (n=10).

Flowchart showing the long-term oxygen treatment group (n=20), the short-term (n=11), and the long-term references (n=10), respectively, were selected.

The characteristics of source cohorts of the study are shown in Table 1, and the final LTOT group with their matched controls are shown in Table 2.
Data collection
At inclusion, all participants completed a self-administered respiratory questionnaire including respiratory symptoms, smoking habits, medical history, and medical treatment. In addition, the patients underwent a clinical examination including COPD assessment test (CAT) [9], examination of lung function, walking distance, electrocardiography, venous blood sampling and arterial blood gases at inclusion as well as at the end of the follow-up. Blood samples were collected at three time points:
- T1: between 8 and 9 a.m. – the intervention group and institutional references.
- T2: between 10 and 12 a.m. – all three groups.
- T3: between 1 and 2 p.m. – the intervention group and institutional references.

Spirometry and reversibility test: Spirometry was performed as recommended by the European Respiratory Society [10] at the respiratory laboratories at Akershus University Hospital and Glittre Hospital. The patients underwent a reversibility test using 400 µg salbutamol. Spirometry was repeated after 15 min to provide post bronchodilator (BD) FEV₁/FVC-ratio to assess the eligibility. Exercise test: In the intervention group and the outpatients, physical exercise capacity was investigated using the incremental shuttle walk test (ISWT) as described by Singh et al. [11]. In the in-hospital rehabilitation group, exercise test was performed using 6 min walking test.

Arterial blood gases: Arterial tension of oxygen (pO2) and carbon dioxide (pCO2) were measured on Radiometer ABL720Flex (Radiometer, Copenhagen, Denmark).

Blood sampling and biochemical assays: Venous blood samples were collected and centrifuged and serum and plasma were aspirated within 60 min, and immediately stored at -80°C for subsequent analyses of cTnT with a high-sensitivity assay (Cobas e 8000 immunoanalyser, Roche Diagnostics, Mannheim, Germany). The lower limit of detection for this assay was 3.0 ng/l. C-reactive protein (Cobas e511/502 system, Roche, Mannheim, Germany) was analysed consecutively and had a lower limit of detection of 3.0 mg/L. Haemoglobin, leukocyte count and creatinine were also analysed consecutively by the hospitals’ routine methods.

Endpoints
The primary endpoint was the change in circulating concentrations cTnT from inclusion to the end of the follow-up (long-term effect by LTOT). The secondary endpoint...
was the serial change in venous cTnT between T1 and T3 (short-term effect of LTOT).

**Statistics**

Demographic data at baseline were analysed using Chi-square, two-sample t-test, and one-way Analysis of Variance as appropriate. Due to a skewed distribution, the main outcome, cTnT, was log-transformed. The data were analysed using propensity score with one-to-one matching with replacement [12]. Briefly, propensity score has been described and defined by Rosenbaum and Rubin to be the probability of treatment assignment conditional on observed baseline covariates [13]. We estimated this probability using logistic regression with LTOT at inclusion as the outcome variable. We developed one model for the short-term effect, and one model for the long-term effect. In both models we included baseline covariates that were associated with the LTOT assignment, i.e. FEV1, COPD assessment test (CAT-score), arterial carbon dioxide tension, shuttle walk distance (only the LTOT-group and the out-patient clinic patients) or associated with cTnT-level at inclusion, i.e. arterial hypertension, history of coronary arterial disease, diabetes, creatinine, and cTnT at inclusion, in the initial model. In addition, we included gender, age, total leucocyte count, and C-reactive protein (CRP) as covariates.

Smoking habits and oxygen tension were not included in the initial models, as they were criteria for LTOT.

The model was then reduced by backward elimination of non-significant covariates provided that the fitted data did not decrease the area under the ROC curve, and the p-value of the Hosmer-Lemeshow test was

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**Table 1** Baseline demographic and clinical data in COPD patients who were candidates for long-term oxygen treatment (LTOT), among COPD patients who participated in outpatient clinic rehabilitation and an institutional rehabilitation program for COPD patients

| Covariates                                      | LTOT (n = 23) | Outpatients (n = 63) | Institutional (n = 118) | p-value |
|-------------------------------------------------|---------------|----------------------|-------------------------|---------|
| Demographic data                                |               |                      |                         |         |
| Female, n (%)                                   | 16 (70)       | 28 (46)              | 67 (54)                 | 0.165   |
| Age, years, mean (sd)                           | 71.9 (7.1)    | 65.8 (7.2)           | 64.1 (7.9)              | <0.001  |
| BMI, kg/m², mean (sd)                           | 25.2 (7.2)    | 25.4 (5.4)           | 24.7 (5.6)              | 0.693   |
| Coronary Heart Disease, n (%)                   | 2 (10)        | 11 (18)              | 12 (10)                 | 0.300   |
| Smoking history                                 |               |                      |                         |         |
| Pack years, mean (sd)                           | 46.0 (31.6)   | 42.3 (20.9)          | 35.0 (18.5)             | 0.020   |
| Current, n (%)                                  | 0 (0)         | 27 (44)              | 23 (19)                 | <0.001  |
| Clinical data                                   |               |                      |                         |         |
| SBP, mmHg, mean (sd)                            | 129 (17.9)    | 132 (28.0)           | 138 (18.4)              | 0.089   |
| Arterial HT, n (%)                              | 14 (61)       | 29 (48)              | 49 (42)                 | 0.234   |
| LTOT-users, n (%)                               | 0 (0)         | 1 (2)                | 13 (11)                 | 0.015   |
| Diabetes mellitus, n (%)                        | 1 (4)         | 10 (16)              | 7 (6)                   | 0.074   |
| Pulmonary function, mean (sd)                   |               |                      |                         |         |
| Spirometry                                      |               |                      |                         |         |
| FVC, Litres                                     | 2.1 (0.79)    | 3.1 (0.96)           | 2.5 (0.87)              | <0.001  |
| FEV1, Litres                                    | 1.0 (0.70)    | 1.5 (0.58)           | 1.1 (0.52)              | <0.001  |
| FEV1/FVC, %                                     | 50 (24)       | 53 (14)              | 44 (10)                 | 0.001   |
| Arterial blood gases                            |               |                      |                         |         |
| Oxygen-tension, kPa                             | 7.6 (1.1)     | 10.6 (2.3)           | 8.9 (1.4)               | <0.001  |
| CO2-tension, kPa                                | 5.6 (0.90)    | 4.9 (0.78)           | 5.7 (0.91)              | <0.001  |
| CAT-score                                       | 22.0 (10.6)   | 19.0 (7.8)           | 18.4 (6.2)              | 0.109   |
| Laboratory data, gm (gsd)                       |               |                      |                         |         |
| Haemoglobin, g/dL                               | 14.3 (2.0)    | 14.3 (1.6)           | 14.5 (1.3)              | 0.575   |
| Leucocytes, 10⁹/L                               | 7.3 (1.5)     | 6.8 (1.7)            | 7.6 (1.3)               | 0.167   |
| C-Reactive Protein, mg/L                        | 5.1 (4.1)     | 3.2 (2.5)            | 2.6 (3.0)               | 0.021   |
| Creatinine, µmol/L                              | 68.2 (1.5)    | 748 (1.2)            | 75.0 (1.2)              | 0.241   |
| cTnT, ng/L                                      | 16.6 (2.8)    | 7.1 (2.2)            | 3.9 (3.4)               | <0.001  |
| Electrocardiogram, n (%)                        |               |                      |                         | 0.738   |
| Pathological Q-wave                             | 3 (13)        | 8 (13)               | 11 (9)                  |         |
| Left Bundle Branch Block                        | 1 (4)         | 1 (2)                | 2 (2)                   | 0.721   |

BMI; Body mass index, SBP: Systolic Blood pressure, HT: Arterial Hypertension, FVC: Forced vital capacity, FEV1: Forced expiratory volume in one second, CAT: COPD assessment test, cTnT: Cardiac troponin T, sd: Standard deviation, gm: geometric mean, gsd: geometric standard deviation
Table 2  Distribution of baseline covariates in the long-term oxygen treatment group, the matched short-term, and the matched long-term references with the corresponding standardised differences (St-D) between the LTOT-group and the references. Note that some of the references are counted several times so that number of observation is 20 in each group (index to references = n to 1)

| Covariates at inclusion | Treatment | Reference groups |
|-------------------------|-----------|-----------------|
|                         | LTOT      | Short-term      | St-D   | Long-term | St-D   |
| Female, N (%)           | 14 (70)   | 15 (75)         | 0.11   | 13 (65)   | 0.15   |
| Age, years, mean (sd)   | 72.5 (6.8)| 70.9 (6.9)      | 0.08   | 71.5 (3.2)| 0.06   |
| Arterial hypertension, n (%) | 10 (60) | 11 (65)         | 0.10   | 7 (44)    | 0.33   |
| Diabetes, n (%)         | 1 (5)     | 0 (0)           | 0.32   | 3 (19)    | 0.44   |
| FEV1, Litres, mean (sd) | 0.93 (0.65)| 0.79 (0.37)   | 0.09   | 1.06 (0.44)| 0.08   |
| ISWT, m, mean (sd)      | 109 (101) | n.a.            | 116 (89)|          | 0.03   |
| CO2-tension, kPa, mean (sd)| 5.7 (0.88)| 5.9 (1.1)    | 0.08   | 5.4 (1.1) | 0.11   |
| CAT-score, mean (sd)    | 23.7 (901)| 24.7 (4.1)     | 0.05   | 21.4 (4.6)| 0.11   |
| Leucocytes, 10⁹/Litres, gm (gsd) | 7.8 (2.9)| 9.2 (4.2)    | 0.15   | 6.5 (1.0) | 0.20   |
| C-Reactive Protein, mg/L, gm (gsd) | 5.1 (4.4)| 5.9 (4.0)    | 0.04   | 2.7 (3.5) | 0.17   |
| Creatinine, µmol/Litres, gm (gsd) | 69.4 (1.5)| 75.3 (1.3)   | 0.08   | 61.6 (1.2) | 0.13   |
| hs-cTnT, ng/L, gm (gsd) | 16.5 (2.7)| 20.7 (4.9)    | 0.06   | 14.0 (2.4)| 0.06   |

sd: standard deviation, FEV1: Forced Expiratory Volume in one second, ISWT: Incremental Shuttle Walk Test, n.a.: not available. CAT: COPD Assessment Test, gm: geometric mean, gsd: geometric standard deviation, CRP: C-Reactive protein, hs-cTnT: high-sensitivity cardiac troponin T

non-significant. The propensity score, i.e. the probability of LTOT, was estimated as the predicted logit from the final model. We developed two propensity score models (ps-models), both with LTOT as the outcome, using covariates from the LTOT-group and the in-patients reference group (ps-model 1), and covariates from the LTOT and the out-patients reference group (ps-model 2).

Thereby, two sets of propensity scores were established.

In each model we used one-to-one matching (pair matching) with replacement, i.e. allowing for many-to-one matches between the referents and the index cases. The lowest difference in propensity score was used as the matching criterion. The similarity of the LTOT group and the matched references was assessed using standardized differences [14]. A standardized difference less than 0.1 indicate negligible differences between the groups [15].

We used the change in cTnT between T1 and T3 as the outcome in the first model (diurnal effect), and the change in cTnT from baseline to follow-up at 3 and 6 months, respectively, in the second model. As there were several cases for each reference, the differences in cTnT-changes between the groups were tested using robust estimates of standard errors. In all these analyses with cTnT as the dependent variable, cTnT we used in the log-transformed form. Furthermore, we used ordinary least square regression with robust standard errors.

Sample size
The sample size was based on our previous study [7]. We considered 25% decrease in cTnT be considered as a clinical meaningful effect of LTOT. We regarded 25% decline in cTnT as a clinical meaningful reduction after commencement of oxygen supplementation. Based on this assumption, we calculated that we needed to include 20 patients in order to detect a reduction in cTnT of 25% with significance level=0.05 and power=0.90. Reference group 1 and 2 were established to adjust for the natural diurnal variation and the long-term change in cTnT, respectively.

All statistical analyses were performed using Stata/SE 15.1, StataCorp LCC, Texas, USA.

Results
Patient characteristics
In the source populations, the LTOT candidates were older and had a more severe smoking history. They had lower lung function, lower arterial oxygen tension, higher carbon dioxide tension, higher CRP and considerably higher cTnT concentrations compare to the reference groups (Table 1).

After matching with replacement it turned out that 10 references in the long-term group and 11 references in the short-term references minimized the difference in propensity score between the LTOT-group and the respective references. Thereby n=11 from the short-term references, and n=10 from the long-term references were used in the final analyses. However, compared with the matched references the differences between LTOT-group and the matched short-term as well as the long-term reference, respectively, were negligible (Table 2).

Moreover, the propensity score models fitted the data well (supplemental Table 1), especially regarding the most significant determinants of LTOT (Table 2). Foremost, the cTnT-level showed an improved similarity between the LTOT-group and both references.

Short-term effects
There was a significant short-term decrease in cTnT from T1 to T2 in both groups combined, as well as in the LTOT group separately, but not in the short-term
references. However, the decline in cTnT from 8 to 9 a.m. to 1–2 p.m. did not differ between the intervention group and short-term references (Table 3).

Long-term effects
There was a numerical increase on cTnT-level in both groups from inclusion to the end of the long-term follow-up. Moreover, the change in cTnT during the follow-up did not differ between the groups (Table 3).

For evaluation of LTOT compliance we assessed the PaO2 levels at T4. PaO2 increased from 7.6 (SD 1.1) kPa to 9.2 (1.7) kPa in the LTOT group (p = 0.002), but was stable in the matched reference group: 10.4 (SD 1.8) kPa at inclusion to 10.3 (SD 1.5) kPa (p = 0.931) at the follow-up.

Discussion
The main finding in our study is that reversing hypoxemia in chronic respiratory failure did not find an association between LTOT and troponin changes on short and long term.

To the best of our knowledge, this is the first study prospectively measuring cTnT in stable COPD patients with chronic respiratory failure before and after LTOT treatment. LTOT-candidates are characterised by severe arterial hypoxemia. It has been suggested that arterial hypoxemia may explain the troponin elevation in these patients, as well as COPD patients in general [16]. Moreover, it is well accepted that elevated troponin is a predictor of mortality in COPD, chronic coronary heart disease, and in general populations [17–19]. We hypothesized that hypoxemia would be the main etiological factor for myocardial damage and thus cTnT levels in COPD. Therefore, we expected that LTOT should reduce the cTnT level. However, in our study cTnT did not decrease within three months after commencement of LTOT. On the contrary, cTnT slightly increased (numerical increase) during these months. Several explanations should be considered: First, low compliance could be a possible explanation. However, all the patients in our study underwent training in using LTOT during their stay in hospital and a follow-up at home. Moreover, they were regularly visited and contacted by phone by an Ambulatory Team consisting of nurses and physical therapist in regards to use of LTOT. Blood tests for cTnT measurements were always collected at the hospital where use of oxygen was carefully checked. Also, a significant increase in PaO2 was recorded in LTOT patients at the follow-up after 3 months [20]. Finally, our hypothesis that oxygen supplementation is associated with a decrease in cTnT may be incorrect. Secondly, the lack of effect of LTOT on cTnT could potentially be explained by irreversible myocardial injury caused by prolonged hypoxemia leading to permanent elevation of troponin level that is unresponsive to oxygen supplementation.

The choice of propensity score as the analytical approach merits some comments. First and foremost, the cTnT-levels as other indices of COPD severity differed greatly between the groups. After matching references to the treatment group, these dissimilarities attenuated markedly. This matching process is driven by the matching rules, whereas the regression adjustment maybe guided by the results such as selection of covariates. However, during the matching process, the majority of the information in the data are not used but it can be claimed that the references that are not used do not contribute with any relevant information. Moreover, matching with replacement result in multiple use of some references thereby increasing the type-I error. This problem was solved using robust standard errors. Matchings with replacement, instead of without replacement is that when the matches are done without replacement the sorting order of the observations would matter to find the matches. This is unfortunate, especially when there are ties in the matches and hence we have no theoretical ground which matches to choose among the ties for the current observation.

Two other observations in this study also merit comments. First, the cTnT concentrations varied through the day with significantly lower concentrations in both groups at midday compared to the morning. Such diurnal variations have been observed in other cohorts as well (Klinkenberg et al., 2016), and may indicate that this is a general phenomenon, characterized by gradually
declining concentrations during daytime followed by rising concentrations at night peaking the early morning hours.

Secondly, during follow up on a long-term basis cTnT increased in both groups. This observation can indicate that the patients’ cTnT level followed the natural course independently of O2-supplementation. Another hypothesis to explain increases of cTnT may be increased systemic inflammation associated with accelerated airflow limitation [21–23], which in the present study was supported by a correlation between CRP levels and FEV1. It has also been suggested that COPD and CVD involve an acceleration of the normal ageing process which links to low-grade chronic systemic inflammation [24]. Elevated cTnT may be an expression for this process independent of hypoxemia.

The main limitation of the study could be the small number of patients treated by LTOT, thereby limiting the external validity of the results. Small samples are liable to sampling bias distorting the results. However, there was a large variability of cTnT in the LTOT group indicating that that the sample was unbiased. Next, the intervention group had elevated cTnT at inclusion. Therefore, a regression to the mean effect should likely reduce cTnT to normal levels but we did not observe such an effect. Moreover, we believe that inclusion of reference groups adjusts for the natural course of troponin during the day and the follow-up.

The study design was not optimal. The follow-up time was different in the LTOT group (3 months) and long-term reference group (6 months). The times were chosen because of practical reasons related to hospital routine control but we do not believe that this difference explains our results. Since the long-term references had a longer observation time than the LTOT group, the potential time bias should be taken into account.

Ideally, the effect of oxygen treatment on cTn should be investigated using a randomised clinical trial (RCT) design. However, LTOT is an established life-saving treatment in COPD with respiratory failure that preclude RCT to investigate if LTOT reduces cTn. Consequently, we believe that some kind of observational design must be chosen.

Conclusion
It is unlikely that LTOT reduce the cTn level in the stable COPD patients with chronic respiratory failure.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12890-022-02169-7.
7. Soyseth V, Bhatnagar R, Holmedahl NH, Neukamm A, Hoiseth AD, Hagve TA, et al. Acute exacerbation of COPD is associated with fourfold elevation of cardiac troponin T. Heart. 2013;99(2):122–6.
8. Emvik G, Bhatnagar R, Holmedahl NH, Neukamm A, Omland T, Soyseth V. Premature Ventricular Complex is More Prevalent During Acute Exacerbated than Stable States of Chronic Obstructive Pulmonary Disease, and Is Related to Cardiac Troponin T. COPD. 2017;14(3):318–23.
9. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2013;34(3):648–54.
10. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(Suppl 16):5–40.
11. Singh SJ, Morgan MD, Scott S, Walters D, Hardman AE. Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax. 1992;47(12):1019–24.
12. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivar Behav Res. 2011;46(3):399–424.
13. ROSENBAUM PR, RUBIN DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70(1):41–55.
14. Austin PC. Goodness-of-fit diagnostics for the propensity score model when estimating treatment effects using covariate adjustment with the propensity score. Pharmacoepidemiol Drug Saf. 2008;17(12):1202–17.
15. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol. 2001;54(4):387–98.
16. Stone IS, Petersen SE, Barnes NC. Raised troponin in COPD: clinical implications and possible mechanisms. Heart. 2013;99(2):71–2.
17. Anthonisen NR, Connell JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med. 2002;166(3):333–9.
18. McGarvey LP, John M, Anderson JA, Zwarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. Thorax. 2007;62(5):411–5.
19. Omland T, de Lemos JA, Holmen OL, Dalen H, Bentj J, Nygård S, et al. Impact of sex on the prognostic value of high-sensitivity cardiac troponin I in the general population: the HUNT study. Clin Chem. 2015;61(4):646–56.
20. Russell-Hallinan A, Glezenva N, Moran B, Das S, Baugh J, Watson C. BS40 Hypoxia induces gene-specific epigenetic modifications in human cardiac fibroblasts. Heart. 2019;105(Suppl 6):A165-A.
21. Donaldson GC, Seemungal TA, Patel IS, Bhowmik A, Wilkinson TM, Hurst JR, et al. Airway and systemic inflammation and decline in lung function in patients with COPD. Chest. 2005;128(4):1995–2004.
22. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD: Eur Respir J. 2009;33(5):1165–85.
23. Miller J, Edwards LD, Agusti A, Bakke P, Calverley PMA, Celli B, et al. Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. Respir Med. 2013;107(9):1376–84.
24. Mercado N, Ito K, Barnes PJ. Accelerated ageing of the lung in COPD: new concepts. Thorax. 2015;70(5):482–9.

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