

## STUDY PROTOCOL

# Influence of frailty on cardiovascular events and mortality in patients with Chronic Obstructive Pulmonary Disease (COPD): Study protocol for a multicentre European observational study

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## Abstract

### Background

Frailty is a clinical state that increases susceptibility to minor stressor events. The risk of frailty is higher in chronic conditions, such as Chronic Obstructive Pulmonary Disease (COPD). Recent studies on COPD have shown that patients living with frailty have an increased risk of mortality. The presence of cardiovascular diseases or conditions are common in COPD and may increase the risk of death.

### Methods

This protocol describes a European prospective cohort study of community-based people, in a stable condition with diagnosis of COPD (as defined by GOLD guidelines) across hospitals in Italy and UK. Frailty prevalence will be assessed using the Clinical Frailty Scale. At 1- and 2-year follow up, primary outcome will be the impact of frailty on the number of cardiovascular events; secondary outcomes: the influence of frailty on cardiovascular mortality, all-cause mortality, and deaths due to COPD. For the primary outcome a zero-inflated Poisson regression will compare the number of cardiovascular events at 1 year. Secondary outcomes will be analysed using the time to mortality.

### Discussion

This multicentre study will assess the association between frailty and cardiovascular events and mortality in population with COPD. Data collection is prospective and includes routine clinical data. This research will have important implications for the management of patients with COPD to improve their quality of care, and potentially prognosis.

## Trial registration number

NCT05922202 ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)).

## Introduction

Frailty is a clinical syndrome that increases vulnerability to stressors due to decline of multiple physiological reserves. People living with frailty are at higher risk of falls, disability, long hospitalisations, access to care homes, and death [1]. There are two principal approaches of identification of frailty: the deficit accumulation model and the phenotype model [1, 2]. Based on these models, different tools have been created and validated to assess frailty in clinical practice [3].

Chronic diseases such as Chronic Obstructive Pulmonary Disease (COPD) increase the risk of frailty [3, 4]. Literature on frailty in COPD have been emerging in the recent years. While frailty is not synonym for ageing, it is well known that people over 65 years are more likely to live with frailty [4]. In addition, prevalence of COPD increases with age [5]. A double probability of being frail has been demonstrated in patients with COPD compared to patients without COPD in the paper of Marengoni et al. The study reported a prevalence of frailty in COPD between 9% and 64% based on the phenotype model and from 9% to 28% using different frailty assessment instruments [6]. Studies have shown that frailty can increase the risk of mortality in patients with confirmed diagnosis of COPD according to GOLD guidelines ([www.goldcopd.org](http://www.goldcopd.org)) [7–12].

Cardiovascular diseases share common risk factors with COPD such as ageing, active smoking, and sedentary lifestyle. COPD and CVD frequently co-exist and are associated with worse outcomes than either condition alone. Additionally, the risk of cardiovascular events is higher after COPD exacerbation [13, 14]. Cardiovascular comorbidities are very common in patients with COPD and can increase the risk of death in this population [5, 15, 16].

The present protocol describes a research study project on patients with COPD to investigate the influence that frailty can have on the risk of cardiovascular events in these patients. The project will assess the association between frailty and cardiovascular mortality, and the relationship between frailty and all-cause mortality and COPD-related mortality. Our team have widely collected data on frailty previously using routinely collected service evaluation level data.

The study has the goal to provide relevant data for clinical practice and management of patients with COPD to improve quality of care, and potentially prognosis, considering a more accurate characterisation of the patient living with COPD.

## Aims

To assess whether frailty correlates with cardiovascular outcomes in patients diagnosed with COPD according to guidelines. The following research questions will be addressed:

1. How many cardiovascular events (including hospital admissions due to cardiovascular cause) at 12 and 24 months in COPD patients living with frailty vs non-frail COPD patients. Coronary artery disease (CAD), aortic disease, peripheral artery disease (PAD), cerebrovascular disease, deep vein thrombosis (DVT) and pulmonary embolism (PE), and arrhythmias were selected as cardiovascular events. The list of ICD-10 codes related to cardiovascular events of special interest for the study protocol is shown in [Table 1](#).
2. How many deaths due to cardiovascular cause at 12 and 24 months in COPD patients living with frailty vs non-frail COPD patients.

**Table 1.**

	ICD-10 code
<b>Coronary artery disease (CAD)</b>	
Angina	I20
Acute Myocardial Infarction (AMI)	I21
Heart failure	I50
<b>Aortic disease</b>	
Aortic aneurysm	I71.2
Abdominal aneurysm	I71.4
<b>Peripheral artery disease (PAD)</b>	I73
<b>Cerebrovascular disease</b>	
Ischemic stroke	I63
Intracranial hemorrhage	I62
Cerebral aneurysm	I67.1
Transient ischaemic attack (TIA)	G45
<b>Deep vein thrombosis (DVT)</b>	I80
<b>Pulmonary embolism (PE)</b>	I26
<b>Other venous embolism and thrombosis</b>	I82
<b>Arrhythmias</b>	
Atrial fibrillation and flutter	I48
Other cardiac arrhythmias	I49

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- How many deaths due to all-cause mortality at 12 and 24 months in COPD patients living with frailty vs non-frail COPD patients.
- How many deaths due to COPD at 12 and 24 months in COPD patients living with frailty vs non-frail COPD patients.
- Prevalence of frailty in COPD.

## Materials and methods

### Study summary

**Table 2** provides the summary of the study information.

### Study design and setting

Study design: Multicentre European observational study. The study follows the STROBE statement for reporting of cohort studies.

**Table 2. Study summary.**

Study Title	Influence of frailty on cardiovascular events and mortality in patients with COPD
Study Design	Observational
Study Participants	COPD outpatients
Planned Size of Sample	320
Follow up duration	24 months
Planned Study Period	24 months
Research Question/Aim(s)	To assess frailty and number of cardiovascular events in adult patients with COPD in stable condition. To correlate frailty with long-term cardiovascular mortality, all-cause mortality, and mortality due to COPD in patients with COPD. The prevalence of frailty in COPD will also be measured.

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Study setting: Two university hospitals and one local health care service in Italy, and university hospital site in the UK that provide care and follow up/scheduled visits for outpatients diagnosed with COPD will participate. The central study team subsequently provided the ethical approval, protocol, central organisation and long-term delivery of the project.

## Study population

**Patient screening.** Patients will be screened for inclusion criteria by the local team in the outpatient setting at each hospital site. The diagnosis of COPD will be according to the GOLD guidelines ([www.goldcopd.org](http://www.goldcopd.org)) and confirmed by a post-bronchodilator  $FEV_1/FVC < 0.70$ .

Principal Investigators (PIs) at each site will have local responsibility for data quality and entry. Data collection will be carried out using the case report form (CRF) presented in the [S1 File](#). Where personal information is collected at each site, it will be kept secure, and maintained. This will involve the creation of a number code for each patient (Patient Identification, PID) that will guarantee data anonymisation.

**Inclusion criteria.** Patients with age  $\geq 40$  years, with diagnosis of COPD of at least 1 year, in stable condition, without acute exacerbation in the last 30 days and/or all-cause hospitalisation in the last month, able to provide their written informed consent, will be included. Patients with concurrent diagnosis of asthma (asthma/COPD overlap syndrome) and alpha-1 antitrypsin deficiency are will also be included.

**Exclusion criteria.** Terminally ill patients, patients with concurrent diagnosis of interstitial lung disease, presence of restrictive pattern on spirometry, no history of smoking habit, not able to provide their written informed consent, will be excluded.

## Power and sample size

Assuming the proportion of those that are not frail (40%), mildly frail (60%) and moderately to severely frail (75%) will exhibit at least one cardiovascular event at 1 year. In order to detect these two comparisons (not frail, versus mildly frail & not frail versus moderately frail), using a chi-squared test with type-1 error = 0.025 and 80% power. We will need a minimum of 320 patients, approximately 120:120:80 for CFS 1–3, 4–5, 6–8 respectively.

## Variables

A SPIRIT [schedule of enrollment, interventions, and assessments](#) is reported in [Fig 1](#).

## Baseline data

➤ Age, sex, educational level, occupation (current or previous), body mass index (BMI, Kg/M<sup>2</sup>), absence of smoking habit or active smoking expressed as pack/years (= number of cigarettes per day multiplied by the number of years the person has smoked/20), years of COPD, GOLD classes (1, 2, 3, 4) and GOLD grades based on GOLD 2011 (A, B, C, D) and GOLD 2023 reports (A, B, E) ([www.goldcopd.org](http://www.goldcopd.org)), frailty score using the Clinical Frailty Scale ([Fig 2](#)), list and number of comorbidities, list and number of drugs taken.

## Cardiovascular events

These will be defined as the following. Any ICD-10 code reported in [Table 1](#) or the following event recorded in the hospital notes at 1 and 2 years will be considered as a cardiovascular event.

TIMEPOINT	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		Close-out
	$-t_1$	Time 0	12 month follow up	24 month follow up	$t_x$
<b>ENROLMENT:</b>					
Eligibility screening	X				-
Informed consent	X				-
Spirometry	X		X	X	-
Allocation		X			-
<b>INTERVENTIONS:</b>	-	-	-	-	-
<b>DATA COLLECTION and ASSESSMENTS:</b>					
<i>Pack/years</i>	X	X			-
<i>Number of years of COPD</i>	X	X			-
<i>GOLD classes</i>	X	X			
<i>GOLD grades 2011</i>	X	X			
<i>GOLD grades 2023</i>	X	X			
<i>Frailty score (CFS)</i>	X	X	X	X	X
<i>Number of comorbidities</i>	X	X			
<i>Number of drugs</i>	X	X			
<i>No. of CV events</i>			X	X	X
<i>No. of all-cause deaths</i>			X	X	X
<i>No. of deaths due to CV cause</i>			X	X	X
<i>No. of deaths due to COPD</i>			X	X	X

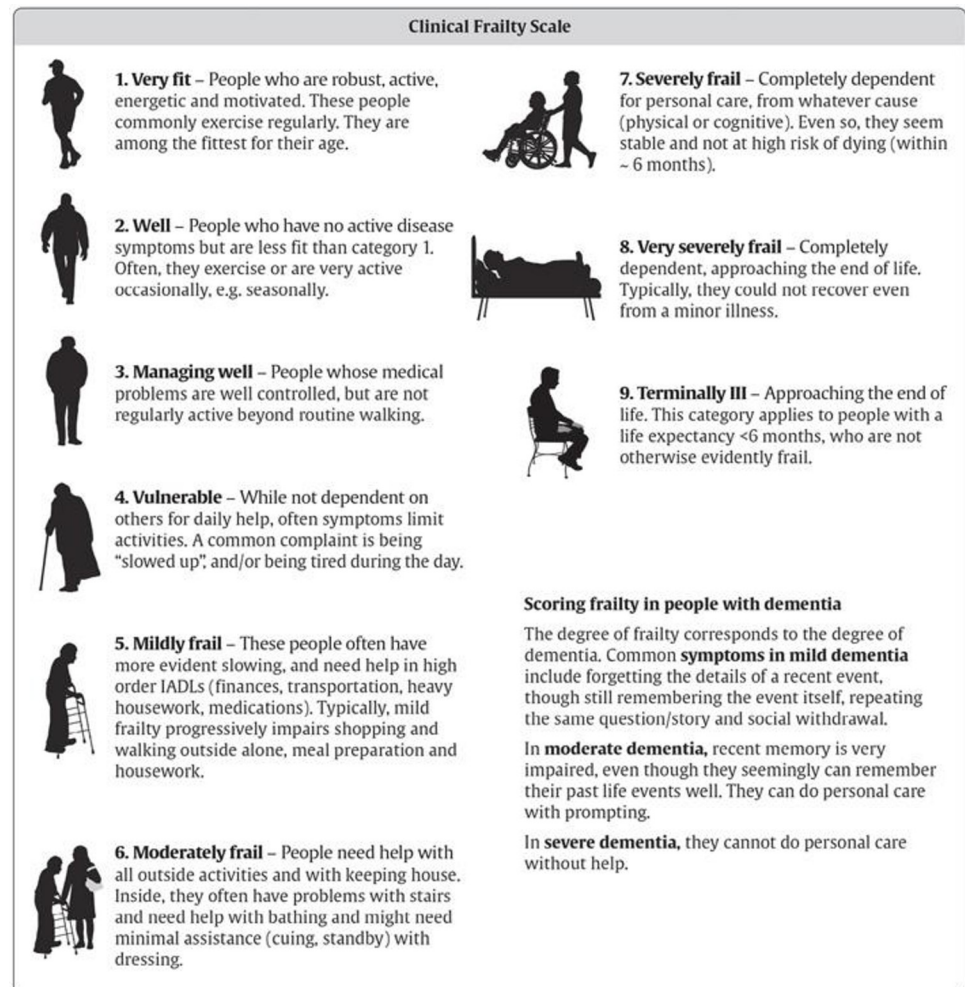
\*The bronchodilation test will be performed only at baseline.

**Fig 1. SPIRIT schedule of enrolment, interventions, and assessments.**

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### Follow up data (12 and 24 months)

- Number of cardiovascular events.
- Number of deaths due to cardiovascular cause.
- Number of all-cause deaths.
- Number of deaths due to COPD.



**Fig 2. Clinical frailty scale.**

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➤ Frailty score using the Clinical Frailty Scale (Fig 2).

➤ Follow up spirometry.

### Frailty assessment

We will use the Clinical Frailty Score. This has been validated for use to assess frailty in older patients [17]. The score ranks from 1 to 9 with a score of  $\geq 4$  being classed as mildly frail, and 4–5 and moderately frailty, and 6 to 9 severely frail to terminally ill. Patients scored CFS 9 (terminally ill) will be excluded. We will use the Montreal Cognitive Assessment (MoCA) test to explore cognitive function [18]. The MoCA is a tool used to assess deficits in different cognitive domains: visuospatial ability, executive function, language, memory, attention, naming, orientation, delayed recall, and abstraction. It is scored out of a total of 30 points and a cut-off of  $\leq 26$  may indicate mild cognitive impairment.

### Safety considerations

Safety reporting/adverse events will be reported by Principal Investigators. However, as this study routinely collected clinical data, there are minimal safety issues expected.

## Primary outcome

- Number of cardiovascular events (including hospital admissions due to cardiovascular cause) at 12 and 24 months in COPD patients living with frailty *vs* non-frail COPD patients.

## Secondary outcomes

- Long-term cardiovascular mortality at 12 and 24 months in COPD patients living with frailty *vs* non-frail COPD patients.
- All-cause long-term mortality at 12 and 24 months in COPD patients living with frailty *vs* non-frail COPD patients.
- Mortality due to COPD at 12 and 24 months in COPD patients living with frailty *vs* non-frail COPD patients.
- Prevalence of frailty in COPD.

## Data management plan, data protection and patient confidentiality

All investigators and trial site staff will comply with the requirements of the Good Clinical Practice (GCP) and Guidelines for Data Processing in the European Union (General Data Protection Regulation-GDPR 679/2016) with regards to the collection, storage, processing and disclosure of personal information.

Where personal information is collected, it will be kept secure, and maintained. This will involve:

- The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- No patient identifiable information will be uploaded or stored on the secure database. Collaborators will anonymise patients by recording patient clinical numbers alongside database numbers in a separate secure spreadsheet to aid the collection of data locally.
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis.
- Confidentiality of data will be preserved when the data are transmitted to co-investigators as patients will be assigned a study ID number.
- Data collected from sites will be via the electronic database, using freely available software such as Microsoft XL. The research team are experienced in data management. This database will be held within University of Modena (Italy) and stored for a minimum of 7 years.
- Data custodian and Chief Investigator is Dr Alessia Verduri.

## Statistical analysis

We will aim to recruit a minimum of 320 patients: across a minimum of 3 sites.

This protocol and analysis plan will be drafted by a medical statistician fully blinded to the outcome data.

Data will be analysed for correlation between frailty and clinical outcomes. The primary analysis will be the number of cardiovascular events (time to event) at 12 and 24 months,



adjusting for sex, age (18–64, 65–80, >80) and frailty at the time of recruitment, and other clinically relevant non-respiratory comorbidities. The number of events will be analysed using a zero-inflated Poisson regression to compare the rates between the three frailty groups. The rate with 95%CI will be presented alongside the p-value. Overdispersion will be assessed and if found to be present robust standard errors will be fitted.

The secondary analyses will assess the time to all-cause mortality, cardiovascular mortality, and mortality due to COPD that will be fitted to compare those classified as frail vs not frail visually using a Kaplan Meier plot. Data will be analysed using a multivariable Cox baseline proportional hazards regression, adjusting for covariates. The time to mortality will be calculated from the date of study entry to the end of follow up. The analyses will be presented as Odds Ratio (adjusted OR) with associated 95% confidence intervals and p-values. Subgroups analyses (age, sex, GOLD classes and grades, comorbidities) will be conducted to assess the grade of frailty. Stata version 18 (or later) will be used.

### Validation data

Validation will be performed by local teams on 25% of data fields for 10% of cases. The validated fields will include key demographic and outcome data.

### Patient and Public Involvement (PPI) group

It will be possible to develop a PPI group of patients who have participated to the study. Towards the end of the study, the coordinator centre will invite a group of patients back to the hospital to discuss their personal opinion about the meaning of the research study.

### Ethics

The study was approved and registered by the University of Modena and Reggio Emilia Ethics Committee Area Vasta Nord Emilia-Romagna (Modena, Italy); approval number 448/2023/OSS/AOUMO–SIRER ID 6390, 14<sup>th</sup> November 2023. The study was opened at each participating site. All participating units must obtain approval from their local Ethics Committee. It is the responsibility of the local study team to ensure that the ethical approvals are in place prior to commencing data collection. The principal investigators at each site will ensure that collaborators act in accordance with local clinical governance and guidelines.

The study has been externally peer reviewed by impartial professionals with relevant expertise (respiratory physicians, geriatricians, statisticians).

In the UK, this study was deemed to be a service evaluation, individually approved for use in the UK hospital site.

The study has been registered within [www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT05922202.

All the participants will provide written informed consent (S1 File).

### Status and timeline of the study

Recruitment of participants began on the 19<sup>th</sup> December 2023 at the Hospital Policlinico in Modena (Italy) and will continue for two years (20<sup>th</sup> December 2025).

### Discussion

This protocol describes a study designed to investigate the influence of frailty on the risk of cardiovascular morbidity and mortality in patients with COPD. The study will also assess whether the frailty status can have an impact on all-cause mortality and death due to COPD.



This study will offer key real world data components to describe the complexity of COPD that is frequently associated with cardiovascular disease or other concomitant chronic diseases sharing common risk factors and playing a role in COPD prognosis. Additionally, patients with COPD have high risk of frailty that can increase their risk of mortality [7–12].

Relevant data collected includes comorbidities and GOLD grades based on the GOLD recommendations 2011 and 2023 ([www.goldcopd.org](http://www.goldcopd.org)) to characterise patient's severity related to risk of exacerbation, hospitalisation, and death. The primary research questions this study will answer are whether the frailty status may be associated with the number of cardiovascular events and long-term cardiovascular mortality in a large, complete population with COPD. Answers to the questions of this longitudinal cohort study will inform chest physicians of the role of frailty in patients with COPD. More broadly, the clinical data collected in outpatient setting, including frailty, can have significant value to predict patient's prognosis. This is a current topic in the field of respiratory research.

One limitation of the study design is the lack of a control group of individuals matched on age, sex, smoking habit, and frailty status, but without COPD. This would be useful to distinguish the potential role of COPD in the risk of development of cardiovascular disease [19].

All data will be reported as a whole cohort. Unit-level data for comparison will be fed back to collaborators to support local service improvement. This project will be submitted for presentation at a national or international Respiratory and Geriatric conference. Manuscript(s) will be prepared following close of the project. Manuscript(s) will also be prepared following interim data analysis at 12 months if numbers of patients recruited to the study at that time reach the planned sample size.

## Supporting information

**S1 File. The SPIRIT checklist, informed consent form, and case report form (CRF) are presented in S1 File.**

(ZIP)

**S2 File.**

(PDF)

## Author Contributions

**Conceptualization:** Alessia Verduri.

**Formal analysis:** Ben Carter.

**Investigation:** Alessia Verduri, Enrico Clini, Jonathan Hewitt.

**Methodology:** Alessia Verduri, Enrico Clini, Ben Carter, Jonathan Hewitt.

**Project administration:** Alessia Verduri, Enrico Clini.

**Software:** Ben Carter.

**Supervision:** Alessia Verduri, Enrico Clini, Ben Carter, Jonathan Hewitt.

**Writing – original draft:** Alessia Verduri.

**Writing – review & editing:** Alessia Verduri, Enrico Clini, Ben Carter, Jonathan Hewitt.

## References

1. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56(3): M146–56. <https://doi.org/10.1093/gerona/56.3.m146> PMID: 11253156

2. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal* 2001; 1:323–36. <https://doi.org/10.1100/tsw.2001.58> PMID: 12806071
3. Clegg A, Young J, Iliffe S, et al. Frailty in elderly people. *Lancet* 2013; 381 (9868):752–62. [https://doi.org/10.1016/S0140-6736\(12\)62167-9](https://doi.org/10.1016/S0140-6736(12)62167-9) PMID: 23395245
4. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013; 14(6): 392–7. <https://doi.org/10.1016/j.jamda.2013.03.022> PMID: 23764209
5. Global Initiative for Chronic Obstructive Lung Disease ([www.goldcopd.org](http://www.goldcopd.org)).
6. Marengoni A Vetrano DL, Manes-Gravina E, et al. The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies. *CHEST* 2018; 154(1):21–40. <https://doi.org/10.1016/j.chest.2018.02.014> PMID: 29477493
7. Luo J, Zhang D, Tang W, et al. Impact of Frailty on the Risk of Exacerbations and All-Cause Mortality in Elderly Patients with Stable Chronic Obstructive Pulmonary Disease. *Clin Interv Aging* 2021; 16:593–601. <https://doi.org/10.2147/CIA.S303852> PMID: 33880018
8. Kennedy CC, Novotny PJ, LeBrasseur NK, et al. Frailty and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* 2019; 16(2):217–224. <https://doi.org/10.1513/AnnalsATS.201803-175OC> PMID: 30433830
9. Lee SY, Nyunt MSZ, Gao Q, et al. Co-occurrence of Physical Frailty and COPD and Association with Disability and Mortality: Singapore Longitudinal Ageing Study. *CHEST* 2022; 161(5):1225–1238. <https://doi.org/10.1016/j.chest.2021.12.633> PMID: 34914976
10. Galizia G, Cacciatore F, Testa G, et al. Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. *Aging Clin Exp Res* 2011; 23:118–125. <https://doi.org/10.1007/BF03351076> PMID: 21743290
11. Lahousse L, Ziere G, Verlinden VJA, et al. Risk of frailty in elderly with COPD: a population-based study. *J Gerontol A Biol Sci Med Sci* 2016; 71(5):689–695. <https://doi.org/10.1093/gerona/glv154> PMID: 26355016
12. Verduri A, Carter B, Laraman J, et al. Frailty and its influence on mortality and morbidity in COPD: a systematic review and meta-analysis. *Intern Emerg Med* 2023; 18(8):2423–2434. <https://doi.org/10.1007/s11739-023-03405-6> PMID: 37668748
13. Dransfield MT, Criner GJ, Halpin DMG, et al. Time-dependent risk of cardiovascular events following an exacerbation in patients with Chronic Obstructive Pulmonary Disease: post hoc analysis from the IMPACT trial. *J Am Heart Assoc* 2022; 11:e024350. <https://doi.org/10.1161/JAHA.121.024350> PMID: 36102236
14. Wang M, Lin EP-Y, Huang L-C, et al. Mortality of cardiovascular events in patients with COPD and preceding hospitalization for acute exacerbation. *CHEST* 2020; 158(3):973–985.
15. Divo M, Cote C, de Torres JP, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186:155–161. <https://doi.org/10.1164/rccm.201201-0034OC> PMID: 22561964
16. Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? *Eur Respir Rev* 2018; 27:180057. <https://doi.org/10.1183/16000617.0057-2018> PMID: 30282634
17. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173(5):489–95. <https://doi.org/10.1503/cmaj.050051> PMID: 16129869
18. Nasreddine ZS, Philips NA, Bedirien V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *JAGS* 2005; 53:695–699.
19. Maclagan LC, Croxford R, Chu A, et al. Quantifying COPD as a risk factor for cardiac disease in a primary prevention cohort. *Eur Respir J* 2023; 62(2):2202364. <https://doi.org/10.1183/13993003.02364-2022> PMID: 37385658