Comorbidities reduce survival and quality of life in COPD with severe lung hyperinflation

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Comorbidities reduce survival and quality of life (QoL) in emphysema patients with severe hyperinflation. Appropriate treatment of anxiety, low body mass index and pulmonary arterial hypertension could lead to a survival benefit and improvement in QoL. https://bit.ly/4aWcK26

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Abstract

Rationale and aim Patients with COPD often present with a significant number of comorbidities, which are thought to be related to a higher mortality risk. Our aim was to investigate the prevalence and impact of comorbidities on survival and quality of life (QoL), specifically in patients with emphysema characterised by severe lung hyperinflation.

Patients and methods Data were prospectively collected from patients who visited our hospital for evaluating their eligibility for a bronchoscopic lung volume reduction treatment and were included in the Groningen Severe COPD cohort (NCT04023409). Comorbidities were patient-reported by a questionnaire and were validated with patients' medical records. QoL was assessed with the St Georges Respiratory Questionnaire.

Results We included 830 COPD patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III and IV. The total number of comorbidities was an independent predictor of survival when adjusting for other factors influencing survival (HR 1.12, 95% CI 1.05–1.20, p<0.001). Of the individual comorbidities, pulmonary arterial hypertension (HR 1.53, 95% CI 1.01–2.32, p=0.045), low body mass index (HR 1.63, 95% CI 1.16–2.27, p=0.004) and anxiety (HR 1.46, 95% CI 1.11–1.92, p=0.007) were independently associated with worse survival. Moreover, patients having 3, 4 or >5 comorbidities had a significantly (all p<0.05) worse QoL, in comparison to patients without comorbidities.

Conclusion Our results show that comorbidities were associated with lower survival and poor QoL in emphysema patients characterised by severe hyperinflation. Appropriate treatment of treatable traits, including anxiety, low body mass index and pulmonary arterial hypertension, could lead to a survival benefit and improvement in QoL in this specific patient population.

Introduction

COPD is the third leading cause of death worldwide and is responsible for ~6% of the total number of global deaths according to the World Health Organization [1]. COPD is a complex and heterogeneous disease, not only characterised by chronic airflow limitation, but also by the frequent occurrence of comorbidities. For example, Vanfleteren *et al.* [2] showed that 97.7% of patients in a pulmonary rehabilitation cohort had one or more comorbidities, and half of the patients had four or more comorbidities.

To date, several studies have been conducted investigating the impact of different comorbidities on clinical outcomes such as survival and quality of life (QoL) in patients with COPD. Comorbidities that are related to a higher risk of mortality include among others ischaemic heart disease, congestive heart failure,

malignancies, pulmonary arterial hypertension, diabetes, low body mass index (BMI) and anxiety [3–7]. Besides the significant impact on survival, QoL and self-reported health status also decrease with an increasing number of comorbidities in patients with COPD [8–10].

Most of these studies have focused on a general COPD population, including all severity stages, and did not specify specific COPD phenotypes. However, the cause of death in COPD seems to be related to the stage of the disease. It was shown that patients with severe COPD were more likely to die from respiratory failure, whereas in patients with earlier stages of COPD, 60% of deaths were related to cardiovascular diseases and lung cancer [11–14]. This might imply that comorbidities play a distinct role in survival in patients with severe emphysema.

The University Medical Centre Groningen (UMCG) has an extensive programme for novel bronchoscopic treatments. Patients with COPD from all areas of The Netherlands are referred to the UMCG to assess their eligibility for a bronchoscopic lung volume reduction (BLVR) treatment. Patients who visited the UMCG between August 2014 and July 2019 have been included in the Groningen Severe COPD cohort (registered at clinicaltrials.gov: NCT04023409), an observational cross-sectional cohort with the main aim to identify clinical phenotypes and endotypes in patients with severe COPD.

To the best of our knowledge, the impact of comorbidities on survival and QoL, specifically in patients with emphysema characterised by severe hyperinflation, has not been investigated to date. The Groningen Severe COPD cohort gave us the opportunity to investigate the prevalence of comorbidities in this specific patient population and their impact on survival and QoL.

Methods

Study population

Patients with severe and very severe COPD, defined as Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) grades III (forced expiratory volume in 1 s (FEV_1) 30–49% of predicted) and IV (FEV_1 <30% of predicted), were selected from the Groningen Severe COPD cohort (NCT04023409) [15]. Patients were excluded in case of FEV_1 >50% of predicted, missing haemoglobin and estimated glomerular filtration rate (eGFR) blood values, missing bioelectrical impedance analysis or a diagnosis of severe asthma (see figure 1). The Groningen Severe COPD cohort was approved by the medical ethical review committee of our hospital, and all patients provided written informed consent (ECnumber: 2014/102).

Definition of comorbidities

Comorbidities were recorded by a self-administered questionnaire regarding comorbidities (based on the LIFELINES Cohort Study [16]). Additionally, comorbidities were validated using the patients' medical records. In total, the presence of 22 individual predefined comorbidities has been evaluated in all patients supplementary table S1). The following six comorbidities were solely based on information derived from medical records: obesity (BMI ⩾30 $kg \cdot m^{-2}$); low BMI (BMI <21 $kg \cdot m^{-2}$); muscle wasting (fat free mass

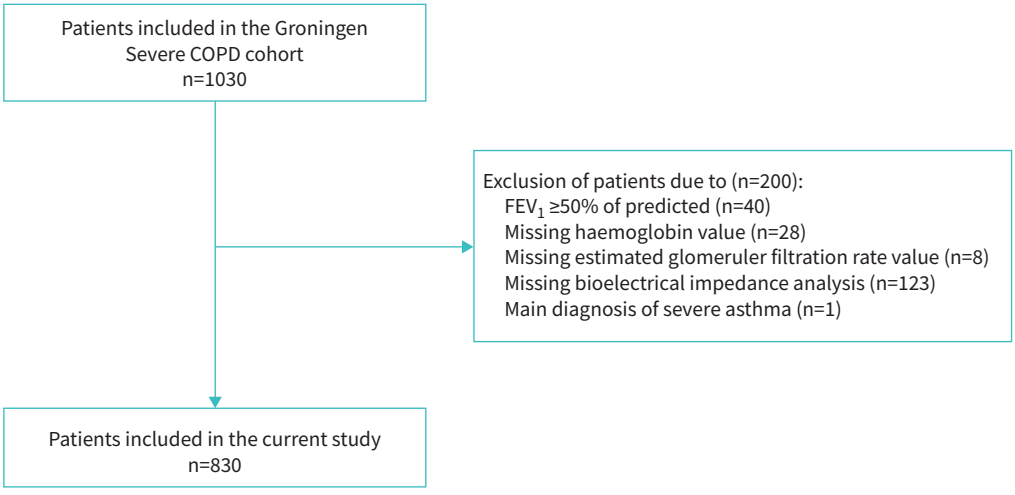

FIGURE 1 Patient inclusion flowchart. FEV_1: forced expiratory volume in 1 s.

index <16 $kg \cdot m^{-2}$ for men, or <15 $kg \cdot m^{-2}$ for women measured by bioelectrical impedance analysis); chronic kidney disease (eGFR <60 mL/min/1.73 m^2); anaemia (haemoglobin level <8.1 $mmol \cdot L^{-1}$ for men or <7.5 $mmol \cdot L^{-1}$ for women); and pulmonary arterial hypertension (right ventricular systolic pressure >35 mmHg measured by cardiac ultrasound or a mean pulmonary arterial pressure >20 mmHg measured by right heart catheterisation if performed on indication in the referring hospital).

The remaining comorbidities were based on a combination of the self-administered questionnaire regarding comorbidities and medical records. A patient was considered to have a specific comorbidity when this was reported by the patient or in case the medical record fulfilled the predefined criteria for this comorbidity. In this, congestive heart failure was defined as a left ventricular ejection fraction <55% with concomitant use of heart failure medication; aortic aneurysm as a thoracic aortic diameter ⩾40 mm [17] or an abdominal aortic diameter ⩾30 mm [18]; immunocompromised state as the use of prednisone ⩾20 $mg \cdot day^{-1}$ for at least 4 consecutive weeks or tumor necrosis factor-α blockers or methotrexate; hypertension as a systolic blood pressure above 140 mmHg or a diastolic blood pressure above 90 mmHg, and the concomitant use of antihypertensive drugs; and hypercholesterolaemia with concomitant use of cholesterol-lowering medication. The other comorbidities, namely myocardial infarction, coronary artery disease, peripheral vascular disease, transient ischaemic attack (TIA), ischaemic cerebrovascular accident, malignant disease, autoimmune disorders, diabetes mellitus, osteoporosis, depression and anxiety, had no measurable definition. These comorbidities were considered to be present if they were mentioned in the medical history or reported by the patient.

Data collection and study measurements

The following measurements were performed during the consultation visit at the UMCG: post-bronchodilator spirometry and body plethysmography according to the European Respiratory Society and/or American Thoracic Society guidelines [19, 20], diffusion capacity, arterial blood gas analysis, bioelectrical impedance analysis, peripheral blood collection including analysis of haemoglobin levels and eGFR, and chest computed tomography (CT) scan (in- and expiration). Quantitative CT analysis was performed using LungQ software (Thirona, Nijmegen, The Netherlands). The St George's Respiratory Questionnaire (SGRQ) [21] and the COPD Assessment Test (CAT) [22] were collected. If a patient underwent a BLVR procedure, this was documented. The vital status of all patients was verified with the Dutch government personal record database at 24 July 2023. Survival time was calculated from the date of the consultation visit in our hospital until the date of death or the date of the vital status verification. As the Groningen Severe COPD cohort is a cross-sectional cohort, no further follow-up measurements were performed.

Statistical analyses

A log-rank test was performed to test which of the individual comorbidities had a significant impact on mortality, and to test whether there was a difference in survival time between patients with less than three comorbidities *versus* patients with three or more comorbidities. A cut-off value of three comorbidities was used as this divided the study population into equal halves. We also examined patient characteristics differences between patients with fewer than three comorbidities and patients with three or more. Cox proportional hazards regression analyses were performed to determine if specific comorbidities independently predicted survival in patients with severe COPD, while adjusting for other survival-influencing factors identified through univariate analysis. Independent samples t-test was used to assess QoL differences between patients with varying numbers of comorbidities and those without comorbidities. All statistical analyses were performed using IBM SPSS Statistics version 28.0.1.0 (IBM, New York, NY, USA) and p-values below 0.05 were considered statistically significant.

Results

Study population

In total, 830 patients with severe COPD were included (figure 1). Patient demographics and clinical characteristics are depicted in table 1. Patients (65% female) had a mean age of 62±7 years. In general, patients were characterised by a mean FEV_1 of 28±8% of predicted with severe hyperinflation (mean residual volume (RV) of 241±55% of predicted, and mean RV/total lung capacity (TLC) ratio of 61% ±8%). Approximately a quarter (27%) of the patients underwent BLVR treatment with endobronchial valves or coils. At the end of the follow-up period, 61% of the patients were still alive with a median follow-up time of 2126 (range 1475–3253) days, and 39% had died with a median follow-up time of 1171 (range 2–3060) days.

Prevalence of comorbidities and their impact on survival

Patients had a median of two (range 0–9) comorbidities. Only 9% of the patients had no comorbidities, 50% had three or more comorbidities and 15% had five or more comorbidities. The most prevalent

TABLE 1 Patient demographics and clinical characteristics (total group n=830)

Demographics	
Sex (female)	537 (65)
Age years	62±7
Pack-years	40 (0–150)
Number of exacerbations in the year before consultation	2 (0–15)
FEV_1 % of predicted	28.3±8.3
GOLD III	322 (39)
GOLD IV	508 (61)
RV % of predicted	241±55
RV/TLC %	60.9±8.4
D_{LCO} % of predicted	34.2±11.1
P_{aCO_2} kPa	5.33±0.72
P_{aO_2} kPa	9.05±1.19
Treated with BLVR	226 (27)
EBV	187 (23)
Coils	39 (5)
Total number of comorbidities	2 (0–9)
SGRQ (total score)	58.9±13.3
CAT (total score)	22.4±6.0
Emphysema score %[#]	36.6±8.4

Data are presented as n (%), mean±SD or median (range). FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{aCO_2}: partial pressure of carbon dioxide; P_{aO_2}: partial pressure of oxygen; BLVR: bronchoscopic lung volume reduction treatment; EBV: endobronchial valves; SGRQ: St George's Respiratory Questionnaire; CAT: COPD Assessment Test. [#]: emphysema score is the percentage of voxels below −950 Hounsfield units on the inspiratory CT scan.

comorbidities were muscle wasting, hypertension, anxiety, depression, osteoporosis, hypercholesterolaemia and atherosclerosis (table 2).

Univariate Cox regression analyses showed that having three (p=0.005), four (p=0.004) or at least five (p<0.001) comorbidities, compared to having no comorbidities at all, was significantly associated with reduced survival (table 2). Moreover, patients with at least three comorbidities had a significantly higher risk of mortality in comparison to patients with less than three comorbidities (figure 2). Of the individual comorbidities, congestive heart failure (p=0.027), pulmonary arterial hypertension (p=0.003), TIA (p=0.032), anaemia (p=0.005), low BMI (p<0.001), muscle wasting (p<0.001) and anxiety (p<0.001) had a significant negative impact on survival. On the contrary, obesity (p=0.048) was significantly associated with a better survival (table 2).

Differences in patient characteristics according to comorbidity count

Patients with at least three comorbidities were predominantly female, older, had a higher RV/TLC ratio, lower diffusion capacity for carbon monoxide (D_{LCO}), higher partial pressure of carbon dioxide (P_{aCO_2}), lower partial pressure of oxygen (P_{aO_2}) and higher CAT total scores compared to patients with less than three comorbidities (table 3). There were no differences in FEV_1, RV, undergoing a BLVR treatment or emphysema score (table 3).

Multivariate predictors of survival

Higher age, higher number of exacerbations in the year before the consultation visit, lower FEV_1, higher RV, lower D_{LCO}, higher P_{aCO_2}, lower P_{aO_2}, higher emphysema score and not undergoing BLVR treatment were significantly associated with a reduced survival rate (supplementary table S2).

These variables were included in a multivariate regression model to evaluate which comorbidities were independent predictors of survival when adjusting for these variables. Due to the limited availability of diffusion capacity measurements, we only included P_{aCO_2} and P_{aO_2} in the model. Additionally, emphysema score was not included due to its correlation with RV and some missing quantitative CT analyses. The multivariate Cox regression model showed that pulmonary arterial hypertension (HR 1.53, 95% CI 1.01–2.32, p=0.045), low BMI (HR 1.63, 95% CI 1.16–2.27, p=0.004) and anxiety (HR 1.46, 95% CI 1.11–1.92, p=0.007) were independently associated with a poorer survival (table 4).

TABLE 2 Prevalence of comorbidities (n=830) and results of univariate Cox regression analysis to investigate the impact of comorbidities on survival

	Prevalence	Exp(B)	95% CI	p-value
Total number of comorbidities		1.161	1.095–1.230	**<0.001**
None	76 (9.2)			
1	135 (16.3)	1.410	0.828–2.401	0.205
2	205 (24.7)	1.445	0.877–2.382	0.148
3	157 (18.9)	2.058	1.246–3.401	**0.005**
4	133 (16.0)	2.122	1.278–3.521	**0.004**
5 or more	124 (14.9)	2.868	1.726–4.765	**<0.001**
Congestive heart failure	27 (3.3)	1.733	1.063–2.825	**0.027**
Pulmonary arterial hypertension	53 (6.4)	1.787	1.226–2.603	**0.003**
Atherosclerosis	174 (21.0)	1.275	0.989–1.644	0.060
Myocardial infarction	48 (5.8)	1.216	0.781–1.893	0.387
Coronary artery disease	97 (11.7)	1.152	0.833–1.594	0.392
Peripheral vascular disease	27 (3.3)	1.188	0.651–2.169	0.574
iCVA	27 (3.3)	1.369	0.786–2.386	0.267
Transient ischaemic attack	66 (8.0)	1.467	1.033–2.084	**0.032**
Aortic aneurysm	28 (3.4)	1.306	0.750–2.275	0.346
Chronic kidney disease	36 (4.3)	0.956	0.560–1.634	0.870
Malignancy	118 (14.2)	1.043	0.763–1.425	0.791
Autoimmune disorder	56 (6.7)	0.796	0.488–1.298	0.360
Immunocompromised	11 (1.3)	0.765	0.245–2.385	0.644
Anaemia	20 (2.4)	2.358	1.290–4.308	**0.005**
Hypertension	278 (33.5)	0.966	0.766–1.218	0.770
Hypercholesterolaemia	188 (22.7)	1.221	0.950–1.570	0.118
Diabetes mellitus	45 (5.4)	1.113	0.713–1.802	0.597
Osteoporosis	203 (24.5)	1.191	0.935–1.518	0.157
Obesity	84 (10.1)	0.636	0.406–0.997	**0.048**
Low body mass index	176 (21.2)	1.864	1.460–2.379	**<0.001**
Muscle wasting	339 (40.8)	1.521	1.222–1.893	**<0.001**
Depression	207 (24.9)	1.213	0.952–1.546	0.118
Anxiety	217 (26.1)	1.549	1.229–1.953	**<0.001**

Prevalence is presented as n (%). Significant values (p<0.05) are depicted in bold. iCVA: ischaemic cerebrovascular accident.

Next, a multivariate regression model was performed, including the total number of comorbidities instead of the individual comorbidities. This model showed that the total number of comorbidities was an independent predictor (HR 1.12, 95% CI 1.05–1.20, p<0.001) of survival, when adjusting for the other factors influencing survival (supplementary table S3).

Impact of comorbidities on QoL

Patients having three (p=0.026), four (p=0.005) or five or more (p=0.002) comorbidities had significantly higher total SGRQ scores, meaning a lower QoL, in comparison to patients with no comorbidities (figure 3). Patients without comorbidities had a mean total SGRQ score of 55.1±12.8 points, whereas patients with five or more comorbidities had a mean total score of 61.7±14.5 points. When looking at the three subdomains of the SGRQ, the worse QoL in patients with at least three comorbidities was caused by worse scores on the subdomains activity and impact on daily life. The scores on the subdomain symptoms did not significantly differ between COPD patients with 1, 2, 3, 4 or >5 comorbidities compared to patients without comorbidities (supplementary table S4).

Discussion

Our results showed that in patients with emphysema characterised by severe hyperinflation, only 9% of patients had no comorbidities, 50% had three or more comorbidities and 15% had at least five comorbidities. The total number of comorbidities was an independent predictor of survival. In addition to this, pulmonary arterial hypertension, low BMI and anxiety were independently associated with worse survival. Moreover, patients having three or more comorbidities had a significantly worse QoL, in comparison to patients without comorbidities.

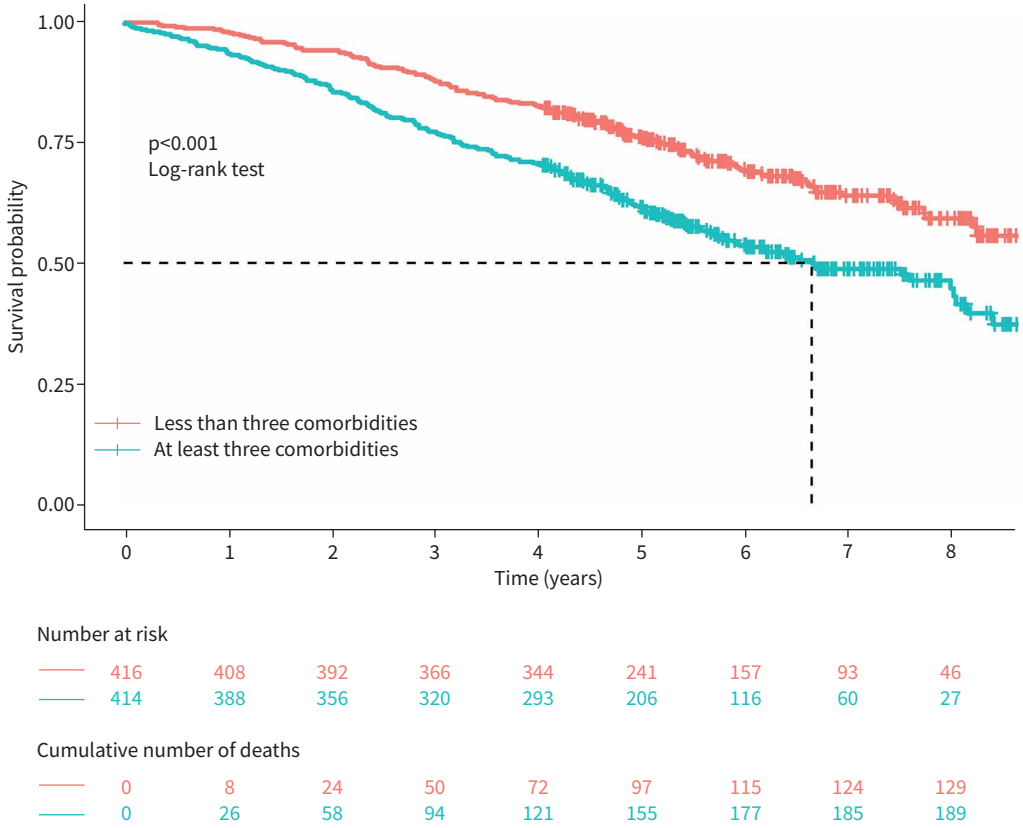

FIGURE 2 Kaplan–Meier curve of survival of patients with less than three comorbidities *versus* patients with at least three comorbidities. Significance was tested using a log-rank test.

Anxiety, low BMI and pulmonary arterial hypertension were independently associated with worse survival in our cohort. These three individual comorbidities are all treatable traits in advanced COPD with possible treatment options [23]. For example, anxiety and malnutrition are two important domains that are addressed during a personalised pulmonary rehabilitation programme [24]. Other possible interventions include pharmacotherapy with anxiolytics, cognitive behavioural therapy, nutritional support and dietary counselling [25, 26]. Posthuma *et al.* [27] recently showed that anxiety was prevalent in almost half of the patients in a similar cohort to ours, and that patients with anxiety were more likely to have a higher SGRQ total score, meaning a worse QoL. Long-term oxygen therapy (LTOT) for >18 h per day is currently the only recommended treatment option for pulmonary arterial hypertension [28]. Reduction in mean pulmonary artery pressure following LTOT was associated with better survival [29]. Screening, diagnosis and treatment of these three treatable traits could therefore enhance survival and QoL in this patient population.

In general, comorbidities that are frequently related to a higher risk of mortality in COPD include cardiovascular diseases, malignancies, diabetes, cachexia and psychological disorders [3–5, 30, 31]. In patients with severe COPD (GOLD stages III and IV), cardiovascular diseases, malignancies, diabetes, impaired renal function and low BMI were related to death from any cause [6, 32, 33]. In our cohort some similarities were found, but also some contradictions to the existing literature. Anxiety and low BMI were independently associated with worse survival in our cohort as well. However, no association was found between malignancies and survival. Moreover, heart failure and coronary artery disease were not predictors of survival in our cohort. This could be explained by the relatively low prevalence of these comorbidities in comparison to other cohorts involving only patients with severe COPD [32, 34]. This is in line with previous findings in a similar cohort to ours, herein only one out of 255 patients had systolic left ventricle dysfunction [35]. Diabetes and chronic kidney disease, with prevalences of 5% and 4% respectively, were also uncommon in our cohort [32]. This could be caused by the fact that our study population consisted of a selected group of patients who were referred to our hospital to evaluate if they were eligible for a BLVR

TABLE 3 Patient characteristics per group based on comorbidity count

	Patients with less than three comorbidities[#]	Patients with at least three comorbidities[¶]	p-value
Demographics			
Sex (female)	236 (57)	301 (73)	**<0.001**
Age years	61±8	63±7	**<0.001**
Pack-years	39 (0–115)	40 (1–150)	0.065
Number of exacerbations previous year	2 (0–14)	2 (0–15)	0.546
FEV_1 % of predicted	28.7±8.4	28.0±8.3	0.184
GOLD III	166 (40)	156 (38)	
GOLD IV	250 (60)	258 (62)	
RV % of predicted	242±55	239±55	0.429
RV/TLC %	59.8±8.2	61.9±8.5	**<0.001**
D_{LCO} mmol·min^{-1}·kPa^{-1}	2.56 (1.07–7.57)	2.32 (1.01–5.66)	**0.009**
P_{aCO_2} kPa	5.24±0.68	5.12±0.75	**<0.001**
P_{aO_2} kPa	9.15±1.15	8.94±1.21	**0.014**
Treated with BLVR	111 (27)	115 (28)	0.755
EBV	90 (22)	97 (23)	
Coil	21 (5)	18 (4)	
CAT (total score)	21.6±6.0	23.2±6.0	**<0.001**
Emphysema score %[+]	36.5±8.1	36.6±8.6	0.832

Data are presented as n (%), mean±SD or median (range). Differences between groups were tested with an independent samples t-test for normally distributed continuous variables, with Mann–Whitney U-test for not normally distributed continuous variables, and with Fisher's exact test for dichotomous variables. Bold p-values represent statistical significance. FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusion capacity of the lung for carbon monoxide; P_{aCO_2}: partial pressure of carbon dioxide; P_{aO_2}: partial pressure of oxygen; BLVR: bronchoscopic lung volume reduction treatment; EBV: endobronchial valves; CAT: COPD Assessment Test. [#]: n=416; [¶]: n=414; [+]: emphysema score is the percentage of voxels below −950 Hounsfield units on the inspiratory computed tomography scan.

treatment. It is less likely that patients with a current malignant disease or cardiovascular disease with a potential risk of death will be referred. On the other hand, the prevalence of psychological disorders was higher and had considerable impact on survival.

TABLE 4 Results of the multivariate Cox regression model (individual comorbidities included)

	HR (Exp(B))	95% CI	p-value
Congestive heart failure	1.320	0.774–2.253	0.308
Pulmonary arterial hypertension	1.530	1.010–2.316	**0.045**
Atherosclerosis	1.052	0.758–1.460	0.760
Anaemia	1.874	0.899–3.907	0.094
Hypercholesterolaemia	1.039	0.751–1.437	0.817
Osteoporosis	1.103	0.839–1.451	0.483
Low body mass index	1.626	1.163–2.271	**0.004**
Obesity	0.623	0.367–1.058	0.080
Muscle wasting	1.179	0.852–1.632	0.320
Depression	1.173	0.876–1.572	0.285
Anxiety	1.457	1.106–1.919	**0.007**
Sex (female)	0.941	0.708–1.250	0.673
Age (years)	1.059	1.038–1.081	**<0.001**
Number of exacerbations previous year	1.065	1.011–1.123	**0.017**
FEV_1 % of predicted	0.972	0.951–0.993	**0.009**
RV % of predicted	1.004	1.001–1.007	**0.004**
P_{aCO_2} kPa	1.042	0.852–1.274	0.688
P_{aO_2} kPa	0.885	0.784–1.007	**0.046**
BLVR (no)	2.029	1.493–2.757	**<0.001**

Significant values (p<0.05) are depicted in bold. HR: hazard ratio; FEV_1: forced expiratory volume in 1 s; RV: residual volume; P_{aCO_2}: partial pressure of carbon dioxide; P_{aO_2}: partial pressure of oxygen; BLVR: bronchoscopic lung volume reduction treatment.

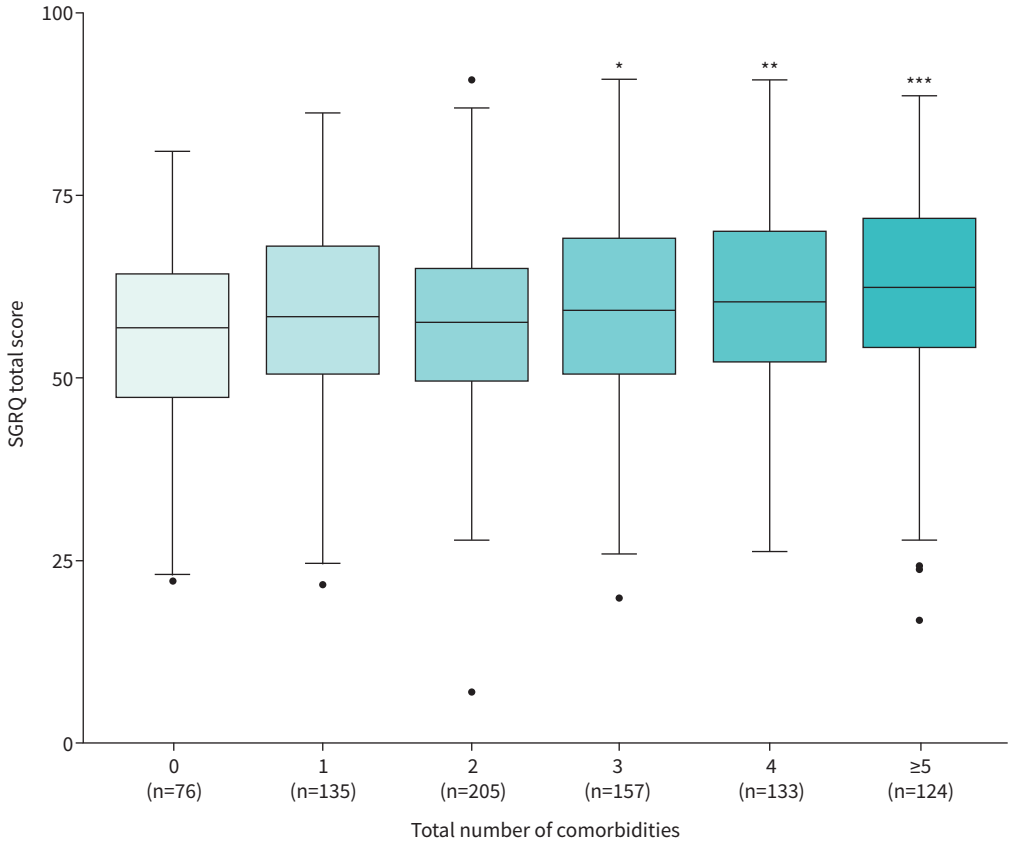

FIGURE 3 Box and whisker plot of St George's Respiratory Questionnaire (SGRQ) total scores according to the total number of comorbidities. SGRQ total scores range from 0 to 100, with higher scores indicating a worse quality of life. n: number of patients per group. *p<0.05 compared with no comorbidities; **p<0.01 compared with no comorbidities; ***p=0.001 compared with no comorbidities.

Vanfleteren *et al.* [2] showed that half of the patients in a pulmonary rehabilitation cohort had four or more comorbidities. The prevalence of comorbidities that we found was considerably lower, with 30% of the patients having at least four comorbidities. This could be due to the fact that Vanfleteren *et al.* actively screened all patients for the presence of comorbidities. Furthermore, patients undergoing pulmonary rehabilitation are more likely to have multimorbidity, whereas patients undergoing a BLVR treatment are less likely to have significant comorbid conditions [36, 37].

Patients having three or more comorbidities had significantly higher total SGRQ scores, reflecting a lower QoL, compared to patients without comorbidities. This was caused by worse scores on the subdomains activity and impact. The scores on the subdomain symptoms, however, did not significantly differ between COPD patients with or without comorbidities. In a study conducted in patients with all COPD stages, having multiple comorbidities was correlated with higher scores on the subdomain activity [38]. Furthermore, in a large cohort of 702 patients with COPD, high scores on the subdomain impact were found to have the largest impairment in health-related QoL [39]. This may suggest that the poorer QoL observed in patients with severe emphysema is more a consequence of the overall clinical picture, including comorbidities, than a result of the respiratory symptoms of COPD itself. Therefore, it is essential to take these comorbidities into account in the treatment of patients with severe emphysema.

The main limitation of our study concerns the method used of assessing and recording of the comorbidities. In our cohort the information on comorbidities was collected from a patient-reported questionnaire, which was subsequently verified using the patients' medical records. However, it is generally known that comorbidities are often under-recognised and under-reported [40]. Therefore, the prevalence of comorbidities in our cohort could be underestimated. To minimalise the risk of underestimation, we combined patient-reported data with medical record-derived data, which also lowered the risk of potential recall bias when focusing solely on patient-reported information. Another limitation is

that our study population consisted of a unique patient population of severe COPD patients referred for a bronchoscopic intervention, which affects the generalisability to the general COPD population. One major strength of our study is the large sample size of a unique patient population from whom data regarding comorbidities was collected, and the relatively long follow-up time of up to 9 years.

In conclusion, our findings indicate that the presence of comorbidities has a negative impact on both survival and QoL in emphysema patients with severe hyperinflation. Appropriate intervention of treatable traits, including anxiety, low BMI and pulmonary arterial hypertension, not only leads to a survival benefit, but also significantly enhances the overall QoL. This emphasises the importance of screening, diagnosis, prevention and treatment of these comorbidities in this specific patient population.

Provenance: Submitted article, peer reviewed.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement: The Groningen Severe COPD cohort was approved by the medical ethical review committee of our hospital and all patients provided written informed consent (EC number 2014/102).

Author contributions: E.A.M.D. ter Haar: conceptualisation, data collection, statistical analysis and writing (original draft, review and editing). D-J. Slebos: conceptualisation and writing (review and editing). K. Klooster: data collection and writing (review and editing). S.D. Pouwels: conceptualisation, writing (review and editing). J.E. Hartman: conceptualisation, data collection, supervision of statistical analysis and writing (review and editing).

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