International Journal of Chronic Obstructive Pulmonary Disease

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ORIGINAL RESEARCH

COPD Severity as an Independent Predictor of Long-Term Survival in Operable Lung Cancer: A Retrospective Analysis from a High-Volume Thoracic Surgery Center

Julia Zimmermann[1], Johannes Schön[1], Valentina Pfeiffer[1], Tim-Mathis Beutel[1], Annalena Felker[1], Elvira Stacher-Priehse[2], Fuad Damirov[1], Niels Reinmuth[3], Rudolf A Hatz[1,4], Christian P Schneider[1,4], Mircea Gabriel Stoleriu[1,4]

[1]Department of Thoracic Surgery, Ludwig-Maximilians-University (LMU) and Asklepios Lung Clinic, Munich and Gauting, Bavaria, Germany; [2]Department of Pathology, Asklepios Lung Clinic, Gauting, Bavaria, Germany; [3]Department of Thoracic Oncology, Asklepios Lung Clinic, Gauting, Bavaria, Germany; [4]Institute for Lung Health and Immunity and Comprehensive Pneumology Center; Helmholtz Center, Munich, Bavaria, Germany

Correspondence: Julia Zimmermann; Mircea Gabriel Stoleriu, Email Julia.Zimmermann@med.uni-muenchen.de; gabriel.stoleriu@helmholtz-munich.de

Purpose: This study aims to identify predictors of long-term survival in patients with chronic obstructive pulmonary disease (COPD) undergoing anatomical resections for non-small cell lung cancer (NSCLC), with focus on COPD severity, to improve perioperative risk stratification and patient care.

Patients and Methods: This retrospective study included all patients with NSCLC and COPD undergoing anatomical resections at the Lung Tumor Center Munich between 2011 and 2020. COPD severity was classified by Global Initiative for Obstructive Lung Disease criteria: Group 1 (mild/moderate obstruction, COPD I–II) and Group 2 (severe obstruction, COPD III–IV). The relationship between COPD severity and perioperative parameters was analyzed using Kaplan-Meier and Cox proportional hazard model.

Results: Of 1663 NSCLC patients undergoing anatomical resections, 476 (28.6%) patients with COPD I–IV (40.5% female, median age 67.28 [60.57; 73.27] years) were included. No significant differences were observed between groups in demographics, topography, TNM classification, histology of the primary tumor, and surgical approach. Group 2 experienced more frequently prolonged mechanical ventilation >2 days (p=0.016), air leaks >5 days (p = 0.020), and arrhythmias (p=0.012). Median overall survival (OS) was reduced in Group 2 (43.73 [30.14; 57.33] vs 85.30 [67.46; 103.14] months, p=0.001). Independent predictors of reduced OS included COPD III–IV (p<0.0001), pT_{3-4} (p=0.007), pN_{1-2} (p<0.0001), preoperative CRP >0.6 mg/dL (p=0.014) and VO_2max <17 mL/min/kg (p=0.040). These predictors increased the risk of death by 1.6 [1.27–1.90], 1.3 [1.06–1.48], 2.1 [1.49–3.03], 1.6 [1.09–2.20] and 1. [1.02–2.00] fold, respectively.

Conclusion: COPD severity independently predicts perioperative morbidity and long-term survival in operable NSCLC patients. Comprehensive assessment of COPD severity can help in identifying high-risk patients and optimizing perioperative care.

Keywords: NSCLC, lung cancer, COPD I–II, COPD III–IV, long-term survival, risk stratification

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide[1] with surgery being the first choice of treatment in appropriate cases. Due to increasing exposure to cigarette smoke, chronic obstructive pulmonary disease (COPD) is reported in 40–70% of lung cancer patients.[2,3] COPD is not only a major risk factor for lung cancer development,[2,4,5] but also increases postoperative morbidity and mortality following lung cancer resection.[6]

Risk stratification in lung cancer is essential for optimizing preoperative patient selection and minimizing post-operative morbidity and mortality. COPD severity assessed by the Global Initiative for Chronic Obstructive Lung Disease staging system (GOLD, grades I–IV)[7] is an important predictor of perioperative morbidity. Specifically, patients

Received: 16 February 2025
Accepted: 20 July 2025
Published: 4 September 2025

with severe COPD (GOLD III–IV) are at a higher risk of poor postoperative outcomes compared to those with mild-moderate disease (GOLD I–II).[8,9]

Previous studies showed that reduced forced expiratory volume in one second (FEV_1) and reduced diffusing capacity of carbon monoxide (DLCO) are significantly associated with postoperative complications and decreased long-term survival in non-small cell lung cancer (NSCLC) patients.[10]

Based on these considerations, preoperative rehabilitation programs aiming the improvement of lung function in COPD patients[11] have gained increasing attention as a potential strategy to enhance postoperative outcomes in high-risk lung cancer patients.[12] This increases the likelihood that lung cancer surgery will achieve positive outcomes in carefully selected patients with severe COPD and can be seen as an increasingly viable treatment option.[13–16] In clinical practice, a careful preoperative evaluation for surgical eligibility routinely includes pulmonary function tests (FEV_1 and DLCO), imaging studies (tumor topography, TNM classification and COPD severity), and the assessment of cardiopulmonary reserve (eg maximum oxygen consumption during physical exertion, VO_2max).

However, high volume studies providing a comparative analysis of COPD severity grades (I–II vs III–IV) in operable lung cancer patients focusing specifically on postoperative short-term and long-term survival are still lacking.

These are extremely important, as the number of lung resections with curative intent is increasing due to optimized surgical techniques. In addition, the prevalence of COPD has also increased, leading to an overall increase in COPD patients undergoing surgery for diagnosed lung cancer. For this high-risk group, it is crucial that perioperative management is continuously optimized.

The present study was conducted in a large thoracic surgery department and aimed to comprehensively characterize operable lung cancer patients with varying degrees of COPD severity (I–IV) in order to gain valuable insights. Known predictors influencing postoperative complications and perioperative outcome were examined in a large cohort and new predictors were identified. In addition, postoperative morbidity, mortality and independent predictors of shortened long-term survival were examined in detail.

Materials and Methods

Study Design and Population

This single center retrospective study was conducted at the Lung Tumor Center Munich, Department of Thoracic Surgery of Asklepios Lung Clinic Gauting, Germany, between January 1st 2011 and December 31st 2020. Ethical approval was obtained from the Ethics Committee of the Ludwig-Maximilians-University Munich (reference number 21-0036). The study included all patients with operable primary NSCLC, undergoing curative anatomical resections (segmentectomy, lobectomy, bilobectomy or pneumonectomy). Patients undergoing anatomical resections for non-malignant lesions and lung cancer patients undergoing wedge resection were excluded. For patients having had more than one tumor resection, only the first operation was considered for analysis purposes. Conversely, patients who did not receive a diagnosis of COPD were excluded from the study (Figure 1).

Data Assessments/Sources

Clinical parameters were extracted from patient files, as well as from the Munich Cancer Registry. Preoperatively, all patients were staged according to the National Comprehensive Cancer Network (NCCN) guidelines.[17] Patients underwent pre- or intraoperative bronchoscopy, pathological lymph node evaluation and FDG-PET/CT scan. Meanwhile, the method of choice for lymph node evaluation was EBUS-TBNA. In the past, a mediastinoscopy was performed in cases of suspected lymph node involvement. Patients with clinical stage II or more also receive a cranial MRI. NSCLC were classified according to the 7th edition of the Tumor Node Metastasis (TNM) staging system[18,19] and The Union for International Cancer Control (UICC),[20] while histopathological specimens were analyzed according to the World Health Organization Classification of lung tumors (2015).[21] The decision regarding the administration of curative surgical therapy, taking into account the tumor stage, performance status and cardiopulmonary condition, was discussed in the interdisciplinary tumor board in accordance with the guidelines.[17]

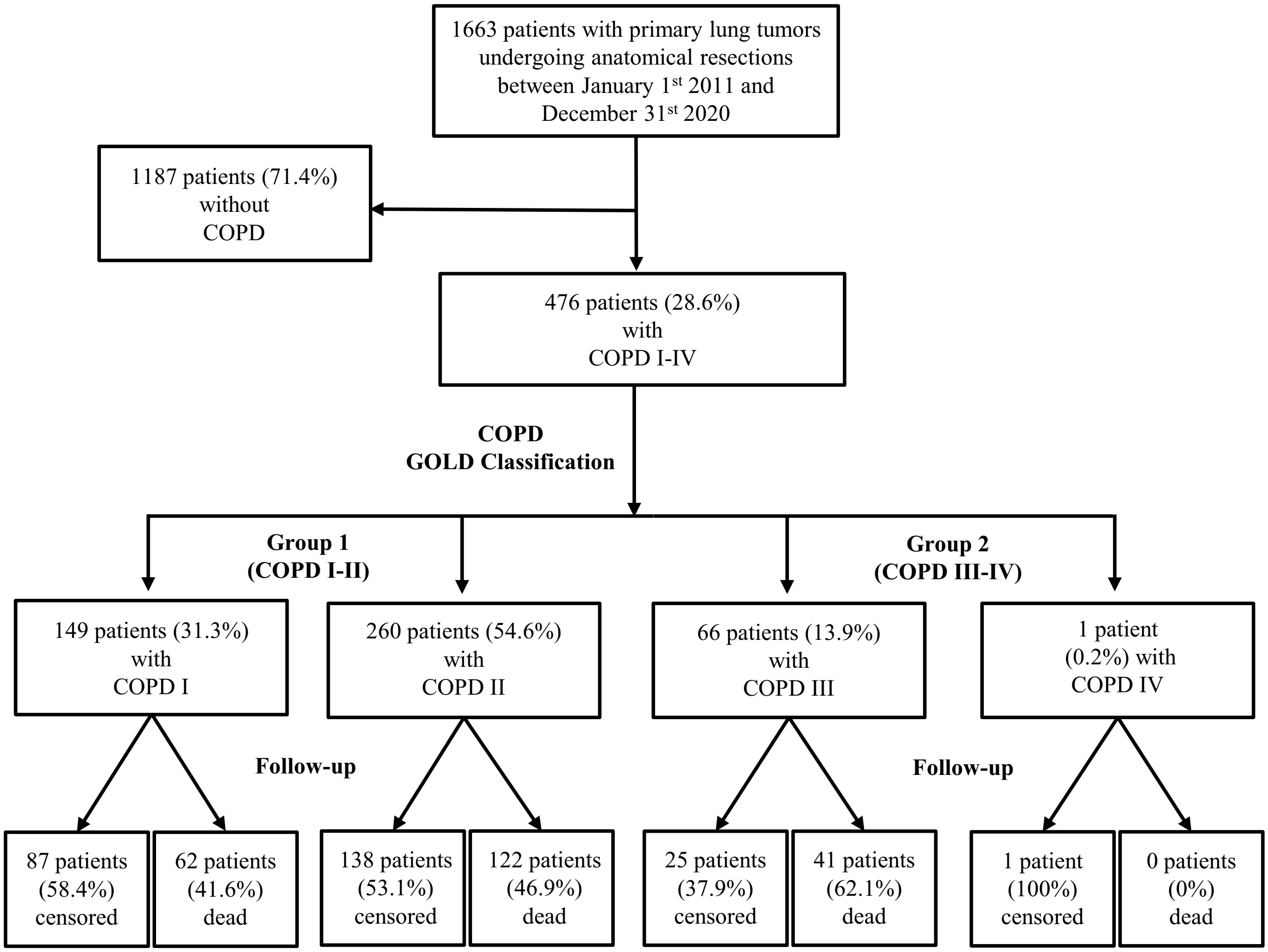

Figure 1 Study flow chart illustrating patient enrollment at study entry. 1663 patients undergoing anatomical resections between January 1st 2011 and December 31st 2020, 1187 (71.4%) patients without COPD were excluded from the study. Thus, 476 patients (28.6%) with operable primary lung tumors and COPD were included. Based on the GOLD classification of COPD,[7] patients were categorized into two groups: Group 1 with mild or moderate obstruction (COPD grade I–II, 409 patients, 85.9%) and Group 2 including patients with severe obstruction (COPD grade III–IV, 67 patients, 14.1%).
Abbreviation: COPD: chronic obstructive pulmonary disease.

Clinical parameters included demographics such as age at resection, sex, body mass index (BMI), smoking status, pack-years (PY), comorbidities, American Society of Anesthesiologists (ASA) Score and the Charlson Comorbidity Index (CCI),[22] laboratory (blood counts, C-reactive protein (CRP), creatinine, lactate dehydrogenase (LDH), albumin, neuron specific enolase (NSE), cytokeratin fraction 21-1 (CYFRA 21-1), carcinoembryonic antigen (CEA), pro-gastrin-releasing peptide (proGRP), respiratory vital capacity (VC), forced expiratory volume in one second (FEV_1), diffusing capacity of the lung for carbon monoxide (DLCO) and maximum rate of oxygen consumption during physical exertion (VO_2max), performed according to the ESTS Guidelines only in patients with impaired lung function (FEV_1 or DLCO<60%). Tumor characteristics were assessed according to the pathological (pTNM) tumor stage, histopathological type, tumor location, as well as tumor grading. Data regarding surgical approach (eg minimally invasive vs open surgery, extent of anatomical resection, surgical and anesthesia time, intraoperative blood loss), as well as postoperative morbidity, intensive care unit (ICU) stay and mortality were collected.

COPD severity was classified according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria based on preoperative spirometry[7] with FEV_1/ FVC<0.7 and FEV_1≥80%/<80%/<50% and /< 30% as a percentage of the predicted value for grade I/II/III and IV, respectively. The diagnosis of COPD and its severity were taken from the patient files.

The follow-up of the patients was carried out in conjunction with regular tumor follow-ups, in accordance with the guidelines.[17] These take place every three months for the first two years after surgery, then every six months until the fifth year and then every year. Patients who received adjuvant therapy postoperatively were followed up during this therapy. With regard to mortality, all patient data was updated with the help of the death register or by contacting patients' relatives.

Endpoints and Outcomes

The primary endpoint of the study was the comparative analysis of clinical parameters stratified by COPD severity in patients with operable NSCLC, to comprehensively characterize the patient cohort with NSCLC and COPD.

The secondary endpoint of the study was the uni- and multivariable survival analysis of operable NSCLC patients in relation to COPD severity, to identify significant predictors for postoperative complications and mortality.

Based on the above-mentioned endpoints, the outcome of the study was defined as long-term overall survival in operable patients with lung cancer and COPD.

Statistical Analysis

Based on GOLD criteria for COPD severity,[7] patients were divided into Group 1 (mild or moderate obstruction, COPD I–II) and Group 2 (severe obstruction, COPD III–IV). A descriptive analysis of clinical demographics, laboratory, lung function and histological parameters was performed. Continuous variables were presented as median and interquartile range (IQRs/ 1st quartile-3rd quartile) or mean (± standard deviations). Group comparisons (COPD I–II vs COPD III–IV) were performed using the Mann–Whitney *U*-test for continuous variables (eg age, BMI, PY, laboratory and lung function parameters) and chi-square or Fisher's exact test for categorial variables (Tables 1–5).

Table 1 Demographic Characteristics of Study Population

Patient Demographics at Study Entry	**Group 1 (COPD I–II) n=409**	**Group 2 (COPD III–IV) n=67**	**p-value**
Age (median, quartiles [1st; 3rd]) years	67.21 [60.31; 73.46]	67.92 [62.40; 72.93]	0.314
Sex (n, %)			
Female	172/409 (42.1%)	21/67 (31.3%)	0.098
Male	237/409 (57.9%)	46/67 (68.7%)	0.098
BMI (median, quartiles [1st; 3rd]) kg/m^2	25.71 [22.44; 29.07]	25.56 [22.02; 29.17]	0.757
Pack years (median, quartiles [1st; 3rd])	40.00 [30.00; 60.00]	45.00 [40.00; 60.00]	0.414
Active smokers (n, %)	164/401 (40.9%)	27/65 (41.5%)	0.922
Comorbidities (n, %)			
Respiratory			
Asthma	16/409 (3.9%)	2/67 (3.0%)	0.712
Pulmonary hypertension	1/409 (0.2%)	1/67 (1.5%)	0.262
Lung fibrosis	7/409 (1.7%)	3/67 (4.5%)	0.143
Previous thoracic surgery	26/409 (6.4%)	6/67 (9.0%)	0.431
Cardiovascular			
Arterial hypertension	224/409 (54.8%)	38/67 (56.7%)	0.766
Atrial fibrillation	24/409 (5.9%)	6/67 (9.0%)	0.335
Ischemic heart disease	64/409 (15.6%)	12/67 (17.9%)	0.639
Myocardial infarction	22/409 (5.4%)	4/67 (6.0%)	0.844

(*Continued*)

Table 1 (Continued).

Patient Demographics at Study Entry	**Group 1 (COPD I–II) n=409**	**Group 2 (COPD III–IV) n=67**	**p-value**
Renal			
Moderate-severe kidney insufficiency	19/409 (4.6%)	2/67 (3.0%)	0.540
Liver			
Slight liver insufficiency	13/409 (3.2%)	0/67 (0.0%)	0.139
Moderate-severe liver insufficiency	7/409 (1.7%)	2/67 (3.0%)	0.478
Neurological			
Cerebrovascular disease	23/409 (5.6%)	2/67 (3.0%)	0.370
Hemiplegia	1/409 (0.2%)	1/67 (1.5%)	0.262
Dementia	1/409 (0.2%)	0/67 (0.0%)	1.000
Diabetes mellitus			
Without organ failure	49/409 (12.0%)	11/67 (16.4%)	0.310
With organ failure	7/409 (1.7%)	1/67 (1.5%)	0.897
Rheumatic disease			
Collagenosis	1/409 (0.2%)	0/67 (0.0%)	1.000
Peripheral vascular disease	41/409 (10.0%)	6/67 (9.0%)	0.786
Non-pulmonary malignancies			
Disseminated Tumor (solid)	1/409 (0.2%)	0/67 (0.0%)	1.000
Lymphoma	5/409 (1.2%)	1/67 (1.5%)	0.854
Charlson Comorbidity Score	7.00 [7.00–8.00]	7.00 [7.00–8.00]	0.143
Lung function parameters (median, quartiles [1st; 3rd])			
VC (predicted, %)	89.00 [78.00–100.00]	75.00 [67.00–90.00]	**<0.0001**
FEV_1 (predicted, %)	70.00 [62.00–81.00]	52.70 [42.25–63.72]	**<0.0001**
DLCO (predicted, %)	63.00 [52.78–76.00]	56.00 [43.35–68.00]	**0.001**
VO_2max (mL/min/kg)	17.20 [14.90–19.50]	15.70 [13.30–17.60]	**0.001**

Notes: Demographic characteristics of lung cancer patients undergoing anatomical resections, stratified by COPD severity. Median and quartiles [1st; 3rd] and absolute values with relative frequency (n, %). Significant p-values are in bold.
Abbreviations: BMI, body mass index (kg/m^2); PY, pack-years; VC, vital capacity; FEV_1, forced expiratory volume in one second; DLCO, diffusing capacity of the lung for carbon monoxide; VO_2max, maximum rate of oxygen consumption during physical exertion.

Table 2 Preoperative Laboratory Parameters of Study Population

Parameters Preoperatively (Median, Quartiles [1st; 3rd])	**Group 1 (COPD I–II) n=409**	**Group 2 (COPD III–IV) n=67**	**p-value**
Blood counts			
Leukocytes (/nL)	8.00 [6.70; 9.45]	8.40 [7.15; 9.95]	0.314
Hemoglobin (g/dL)	13.70 [12.60; 14.80]	13.70 [12.55; 15.05]	0.620
Clinical chemistry			
CRP (mg/dL)	0.46 [0.20; 1.38]	0.62 [0.20; 1.49]	0.663
Creatinine (mg/dL)	0.90 [0.80; 1.10]	0.90 [0.80; 1.10]	0.635
Albumin (g/dL)	3.80 [3.50; 4.00]	3.75 [3.50; 3.93]	0.578
LDH (IU/L)	188.00 [168.50; 219.50]	201.50 [174.25; 228.75]	0.280
NSE (ng/mL)	16.90 [14.15; 20.25]	16.85 [14.28; 18.65]	0.249
CYFRA 21-1 (ng/mL)	2.00 [1.40; 3.50]	1.90 [1.33; 3.45]	0.464
CEA (ng/mL)	3.95 [2.30; 7.10]	4.40 [2.90; 6.65]	0.309
proGRP (pg/mL)	43.20 [33.00; 56.60]	40.00 [31.50; 59.00]	0.719

Notes: Preoperative laboratory parameters of lung cancer patients undergoing anatomical resections, stratified by COPD severity. Continuous variables were presented as median and quartiles [1st; 3rd].
Abbreviations: CRP, C-reactive protein; LDH, lactate dehydrogenase; NSE, neuron specific enolase; CYFRA 21-1, cytokeratin fraction 21-1; CEA, carcinoembryonic antigen; proGRP, pro-gastrin-releasing peptide.

Table 3 Pathological Characteristics of Study Population

Tumor Characteristics	Group 1 (COPD I–II) n=409	Group 2 (COPD III–IV) n=67	p-value
Tumor side (n, %)			
Left	171/409 (41.8%)	25/67 (37.3%)	0.488
Right	238/409 (58.2%)	42/67 (62.7%)	0.488
Tumor localization (n, %)			
Left upper lobe	107/409 (26.2%)	19/67 (28.4%)	0.706
Left lower lobe	56/409 (13.7%)	6/67 (9.0%)	0.286
Right upper lobe	139/409 (34.0%)	23/67 (34.3%)	0.956
Middle lobe	22/409 (5.4%)	5/67 (7.5%)	0.494
Right lower lobe	72/409 (17.6%)	14/67 (20.9%)	0.516
Combined/centrally located	8/409 (2.0%)	0/67 (0.0%)	0.248
TNM7 classification (n, %)			
pT_1	120/371 (32.3%)	23/64 (35.9%)	0.572
pT_2	165/371 (44.5%)	29/64 (45.3%)	0.901
pT_3	58/371 (15.6%)	10/64 (15.6%)	0.999
pT_4	28/371 (7.5%)	2/64 (3.1%)	0.197
Lymph node involvement (n, %)			
pN_0	274/407 (67.3%)	50/67 (74.6%)	0.234
pN_1	81/407 (19.9%)	8/67 (11.9%)	0.122
pN_2	52/407 (12.8%)	9/67 (13.4%)	0.882
$pN_{1\text{-}2}$	133/407 (32.7%)	17/67 (25.4%)	0.234
Metastasis (n, %)			
cM_0	390/407 (95.8%)	67/67 (100.0%)	0.088
cM_1	17/407 (4.2%)	0/67 (0.0%)	0.088
UICC stage (n, %)			
I	200/398 (50.3%)	36/67 (53.7%)	0.598
II	89/398 (22.4%)	19/67 (28.4%)	0.282
III	95/398 (23.9%)	12/67 (17.9%)	0.284
IV	14/398 (3.5%)	0/67 (0.0%)	0.119
Histology of the primary tumor (WHO, n, %)			
Adenocarcinoma	218/407 (53.6%)	34/67 (50.7%)	0.669
Squamous cell carcinoma	143/407 (35.1%)	29/67 (43.3%)	0.199
Large cell carcinoma	26/407 (6.4%)	1/67 (1.5%)	0.109
Carcinoid	6/407 (1.5%)	2/67 (3.0%)	0.374
Others subtypes	14/407 (3.4%)	1/67 (1.5%)	0.399
Differentiation grade of the primary tumor			
G_1	7/361 (1.9%)	1/63 (1.6%)	0.850
G_2	176/361 (48.8%)	34/63 (54.0%)	0.445
G_3	171/361 (47.4%)	26/63 (41.3%)	0.370
G_4	7/361 (1.9%)	2/63 (3.2%)	0.530

Notes: Pathological characteristics of resected lung cancer specimens, stratified by COPD severity. Median and quartiles [1st; 3rd] and absolute values with relative frequency (n, %).
Abbreviations: pTNM, Tumor node metastasis (TNM) staging system applied for intraoperative histopathological specimens;[19] UICC, Tumor staging according to The Union for International Cancer Control.[20]

Table 4 Technical Aspects of the Surgical Approach

Features of the Surgical Approach	**Group 1 (COPD I–II) n=409**	**Group 2 (COPD III–IV) n=67**	**p-value**
Resection side (n, %)			
Left	171/409 (41.8%)	25/67 (37.3%)	0.488
Right	238/409 (58.2%)	42/67 (62.7%)	0.488
Surgical approach (n, %)			
Open (thoracotomy)	263/409 (64.3%)	37/67 (55.2%)	0.154
Minimally invasive (VATS)	101/409 (24.7%)	21/67 (31.3%)	0.248
Conversion to open	45/409 (11.0%)	9/67 (13.4%)	0.561
Resection extent (n, %)			
Segmentectomy	16/409 (3.9%)	11/67 (16.4%)	**<0.0001**
Lobectomy	348/409 (85.1%)	55/67 (82.1%)	0.528
Multilobar - Bilobectomy	25/409 (6.1%)	1/67 (1.5%)	0.123
- Pneumonectomy	20/409 (4.9%)	0/67 (0.0%)	0.064
Surgery time (median, quartiles [1st; 3rd]) (minutes)	182.00 [145.25; 220.00]	187.50 [142.25; 225.50]	0.964
Anaesthesia time (median, quartiles [1st; 3rd]) (minutes)	245.00 [208.75; 284.00]	245.00 [210.00; 290.00]	0.898
Intraoperative blood loss (median, quartiles [1st; 3rd]) (mL)	400.00 [300.00; 500.00]	300.00 [300.00; 500.00]	0.423

Notes: Technical aspects of the surgical approach in lung cancer patients undergoing anatomical resections, stratified by COPD severity. Median and quartiles [1st; 3rd] and absolute values with relative frequency (n, %). Significant p-values are in bold.
Abbreviation: VATS, video-assisted thoracoscopic surgery.

Table 5 Postoperative Morbidity and Mortality of Study Population

Postoperative Morbidity and Mortality	**Group 1 (COPD I–II) n=409**	**Group 2 (COPD III–IV) n=67**	**p-value**
Chest Tube management			
Whole amount of pleural effusion (mL)	1950.00 [1250.00; 2745.00]	1900.00 [1400.00; 3165.00]	0.436
Prolonged air leak (chest tubes, > 5 days)	35/403 (8.7%)	12/67 (17.9%)	**0.020**
Time until removal of the last chest tube (days)	6.0 [5.00; 8.00]	6.0 [5.00; 10.00]	0.309
Postoperative complications (n, %)			
Pneumonia	65/404 (16.1%)	18/67 (26.9%)	0.032
ARDS	1/404 (0.2%)	0/67 (0.0%)	1.000
Bronchial Stump insufficiency	0/404 (0.0%)	0/7 (0.0%)	
Acute pulmonary embolism	3/404 (0.7%)	0/67 (0.0%)	1.000
Re-intubation	20/403 (5.0%)	6/67 (9.0%)	0.186
Invasive ventilation > 2 days	15/403 (3.7%)	7/67 (10.4%)	**0.016**
Tracheotomy	2/404 (0.5%)	1/67 (1.5%)	0.370
Arrhythmias	33/404 (8.2%)	12/67 (17.9%)	**0.012**
Myocardial infarction	0/404 (0.0%)	0/7 (0.0%)	
Empyema	3/404 (0.7%)	0/67 (0.0%)	1.000
Wound infection	5/404 (1.2%)	3/67 (4.5%)	0.057
TIA/ Stroke	3/404 (0.7%)	0/67 (0.0%)	1.000
Hoarseness (RNL paralysis)	5/404 (1.2%)	1/67 (1.5%)	0.863
Chylothorax	3/404 (0.7%)	0/7 (0.0%)	1.000
Delirium > 3 days	3/404 (0.7%)	1/67 (1.5%)	0.460

(*Continued*)

Table 5 (Continued).

Postoperative Morbidity and Mortality	Group 1 (COPD I–II) n=409	Group 2 (COPD III–IV) n=67	p-value
Length of stay (median, quartiles [1st; 3rd]) (days)			
In-hospital stay	15.0 [12.0; 20.0]	18.0 [15.0; 27.0]	**0.0004**
ICU-stay	1.0 [1.0; 1.0]	1.0 [1.0; 1.0]	0.956
Re-Admission ICU	29/404 (7.2%)	9/67 (13.4%)	0.082
Mortality during Follow-up (n, %)	184/409 (45.0%)	41/67 (61.2%)	**0.014**
Overall survival (median, quartiles [1st; 3rd], months)	49.77 [16.53; 86.72]	36.57 [9.50; 64.60]	**0.039**
30 days upon surgery	361/367 (98.4%)	61/61 (100.0%)	0.315
90 days upon surgery	353/364 (97.0%)	59/60 (98.3%)	0.558

Notes: Postoperative morbidity and mortality in lung cancer patients undergoing anatomical resections, stratified by COPD severity. Median and quartiles [1st; 3rd] and absolute values with relative frequency (n, %). Significant p-values are in bold.
Abbreviations: ARDS, acute respiratory distress syndrome; TIA, transient ischemic attack; RNL, recurrent laryngeal nerve; ICU, intensive care unit.

Univariate survival analysis evaluated overall survival (OS) and disease-free survival (DFS). OS was defined as time from surgical resection of the lung tumor to the last contact (censoring) or death (event). DFS was defined as the time interval between lung resection and the first documented relapse. Long-term survival probabilities were calculated using Kaplan–Meier survival analysis by using Log rank test (Mantel-Cox, Figures 2 and 3).

A multivariable survival analysis was performed by Cox proportional hazard model to investigate the independent predictive role of COPD severity and other clinical parameters on survival (Figure 4, Table 6 and Supplementary Table S1). This analysis was reproduced using three selection methods (Enter, Forward Likelihood Ratio/Forward LR and Backward Likelihood Ratio/Backward LR) and validated using decision tree analysis with two independent algorithms (Classification and Regression Trees (CRT) and Quick, Unbiased, Efficient Statistical Tree (QUEST), Figure 4). Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated for independent predictors. Cut-off values were derived using receiver-operator characteristics (ROC) analysis and the Youden criterion. All analyses were performed after excluding missing data from the database using SPPS software (Version 26, IBM, Armonk, New York, USA). P-values <0.05 were considered as statistically significant.

Results

Study Population

The patient selection process is depicted in Figure 1. Of 1663 patients admitted for anatomical resections of the primary lung tumor, 476 patients with COPD (193/40.5% female, 283/59.5% male, median age 67.28 [60.57; 73.27] years) were included. 149 patients (31.3%) had a history of COPD I, 260 patients (54.6%) COPD II, 66 patients (13.9%) COPD III and one patient (0.2%) COPD IV. Group 1 (COPD I–II) comprised 409 patients (85.9%) and Group 2 (COPD III–IV) 67 patients (14.1%).

Demographic Characteristics

Patient demographics are presented in Table 1. The entire cohort was characterized by a homogenous BMI 25.66 [22.44; 29.07] kg/m^2 and nicotine consumption (40.1% active smokers, 40.00 [30.00; 60.00] PY) without significant differences between groups. Isolated or combined comorbidities, as assessed by CCI,[22] were not significantly associated with COPD severity in both groups. While lung function parameters were significantly lower in Group 2 (COPD III–IV, Table 1), preoperative laboratory parameters were not associated with COPD severity (Table 2).

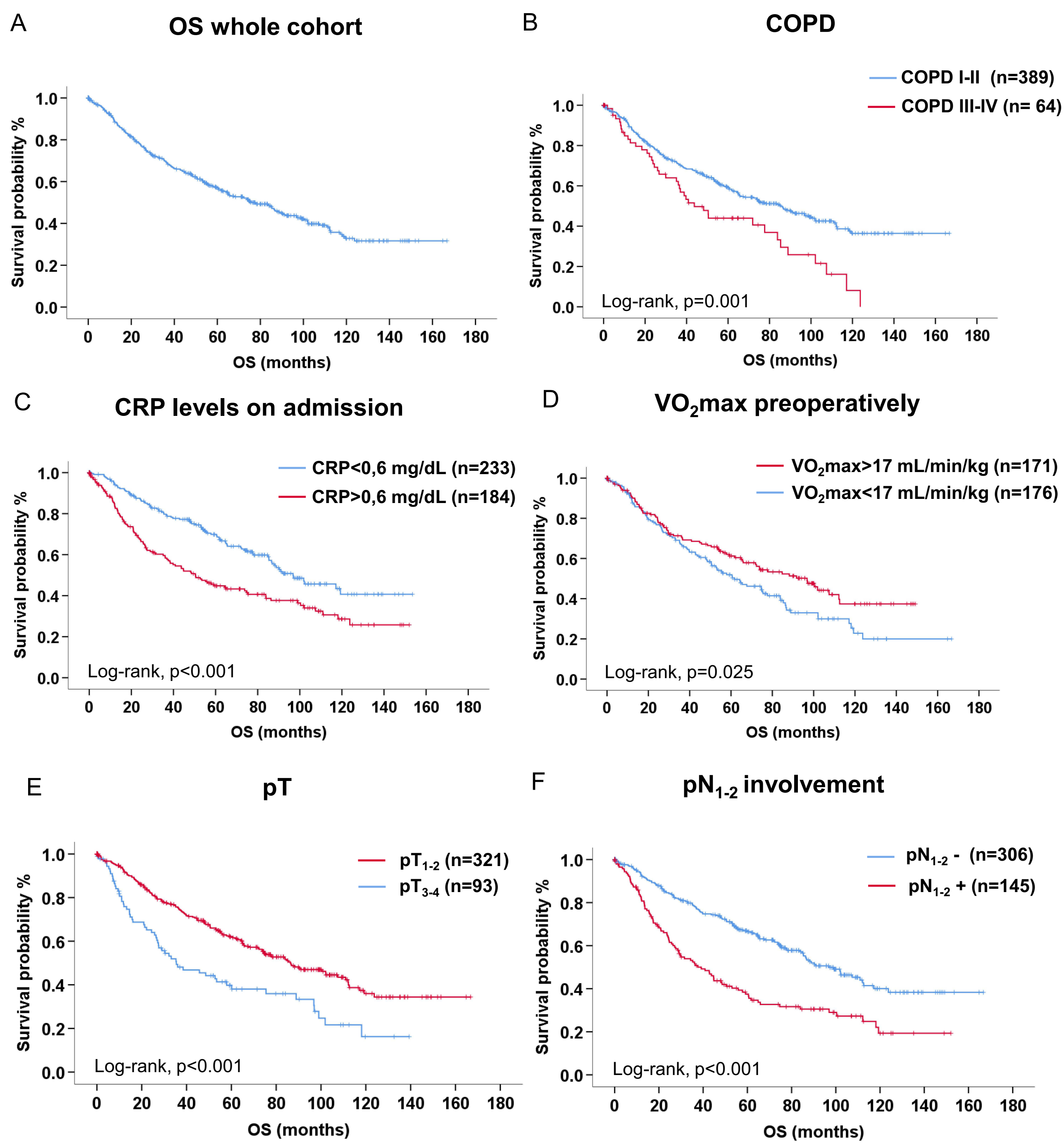

Figure 2 Kaplan–Meier survival analysis including patients at risk, reported events (death) and patients censored (October 2024) illustrating the overall survival of the whole cohort (**A**), according to COPD severity (**B**), serum C-reactive protein levels on admission preoperatively (**C**), VO_2max preoperatively (**D**), tumor stage of the intraoperative specimens (**E**), as well as hilar or mediastinal lymph node involvement of the intraoperative specimens (**F**). Comparison of the survival estimates was analyzed by Log rank test. Values of p<0.05 were considered significant.

Abbreviations: OS, overall survival; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; VO_2max, maximum rate of oxygen consumption during physical exertion; pT, tumor stage of the intraoperative specimens according to the TNM7;[19] pN_{1-2}+, hilar or mediastinal lymph node involvement of the intraoperative specimens according to the TNM7.[19]

Primary Tumor Characteristics and Surgical Approach

The primary tumor characteristics are summarized in Table 3. Tumors were homogenously distributed on both sides of the lungs, irrespective of COPD severity (right side 58.2% in Group 1 and 62.7% in Group 2). The most common tumor localization was the upper lobes (right upper lobe 34.0% in Group 1 and 34.3% in Group 2; left upper lobe 26.2% in

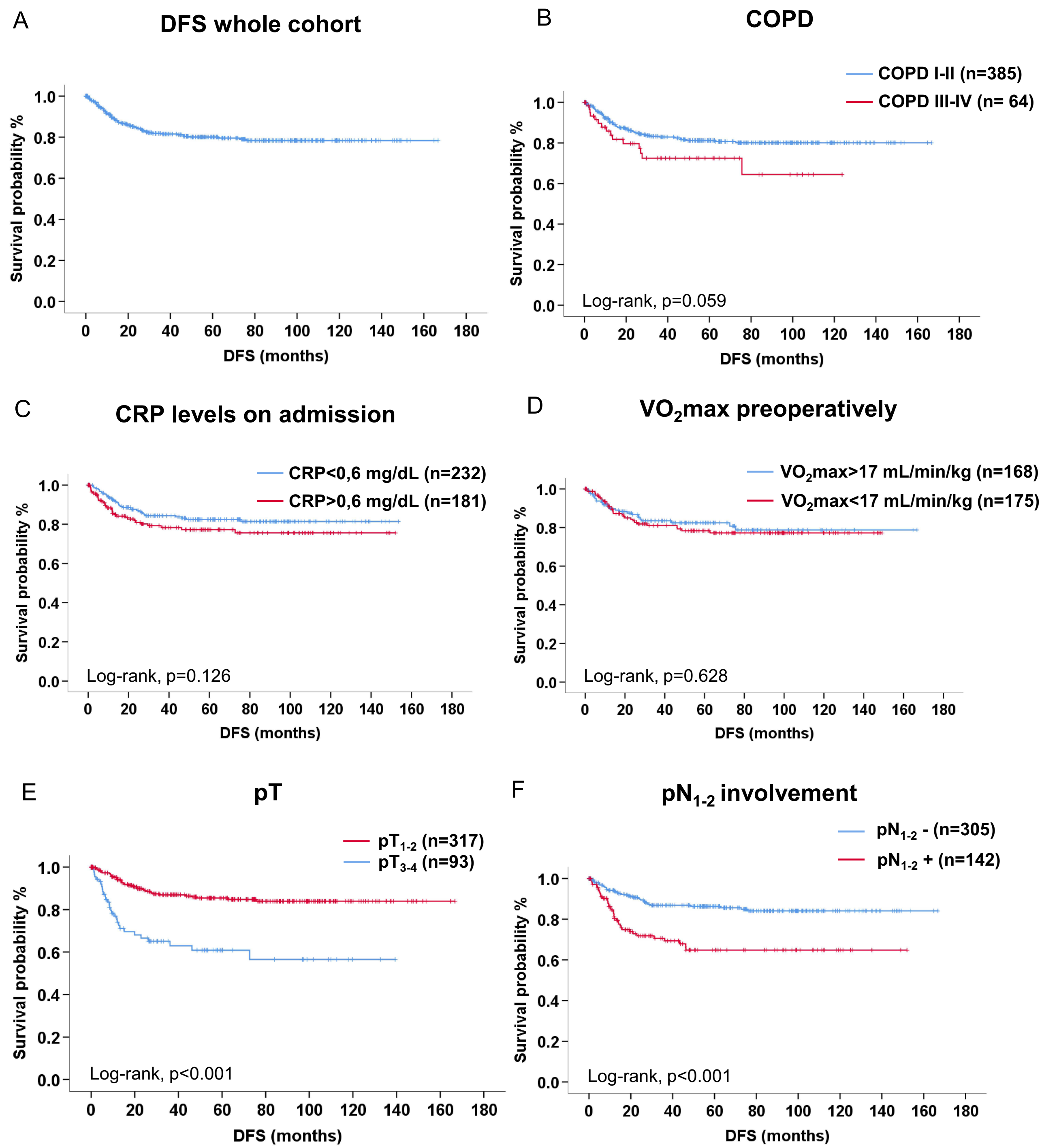

Figure 3 Kaplan–Meier survival analysis including patients at risk, reported events (death) and patients censored (October 2024) illustrating the disease-free survival of the whole cohort (**A**), according to COPD severity (**B**), serum C-reactive protein levels on admission preoperatively (**C**), VO_2max preoperatively (**D**) tumor stage of the intraoperative specimens (**E**), as well as hilar or mediastinal lymph node involvement of the intraoperative specimens (**F**). Comparison of the survival estimates was analyzed by Log rank test. Values of p<0.05 were considered significant.

Abbreviations: DFS, disease-free survival; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; VO_2max, maximum rate of oxygen consumption during physical exertion; pT, tumor stage of the intraoperative specimens according to the TNM7;[19] $pN_{1\text{-}2}$+, hilar or mediastinal lymph node involvement of the intraoperative specimens according to the TNM7.[19]

Group 1 and 28.4% in Group 2). A homogenous distribution for all tumor stages ($pT_{1\text{-}4}$) was reported, with pT_2 being the most frequent stage (44.5% in Group 1 and 45.3% in Group 2), corresponding to UICC stage I (50.3% in Group 1 and

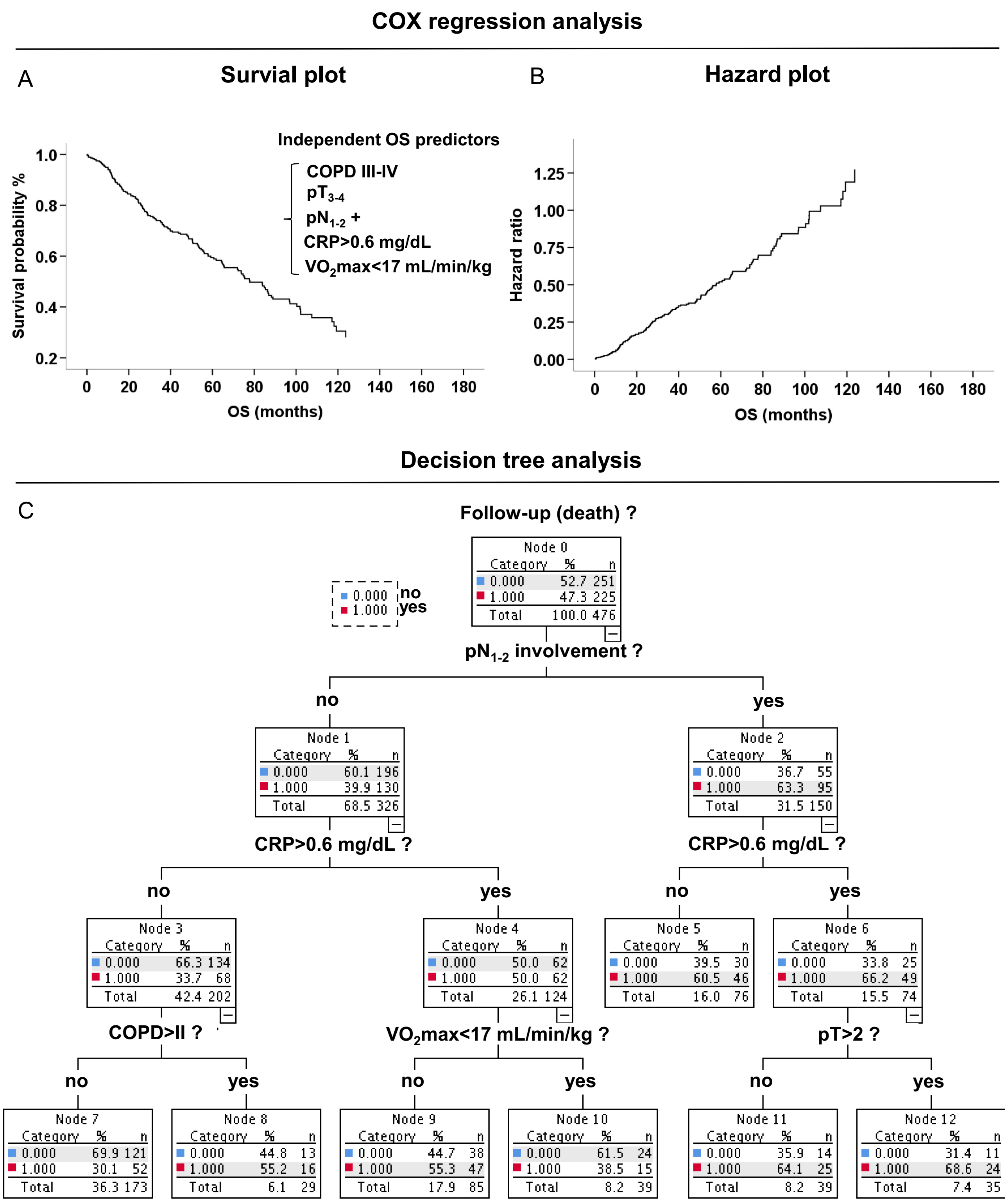

Figure 4 Multivariable Cox proportional hazard model including patients at risk, reported events (death) and patients censored (October 2024) illustrating the survival plot (**A**) and hazard plot (**B**) of patients experiencing COPD III–IV, large tumors (pT_{3-4}), hilar or mediastinal lymph node involvement (pN_{1-2}+), serum CRP>0.6 mg/dL and VO_2max<17 mL/min/kg as significant independent predictors of worse long-term OS. Decision tree analysis including the independent predictors of OS with absolute values (n) and percentages indicating death events for each condition/ node (**C**). Cox regression analysis was performed by Enter, Forward Likelihood Ratio and Backward Likelihood Ratio selection methods. Decision tree analysis was performed using two algorithms (Classification and Regression Trees/CRT; Quick, Unbiased, Efficient Statistical Tree/ QUEST).

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein levels; VO_2max, maximum rate of oxygen consumption during physical exertion; pT, tumor stage of the intraoperative specimens according to the TNM7;[19] pN_{1-2}+, hilar or mediastinal lymph node involvement of the intraoperative specimens according to the TNM7.[19]

Table 6 Cox Proportional Hazard Regression Analysis

Independent Predictors of Survival	Exp (B) [95% CI]	P-value
COPD severity (grade I–II vs III–IV)	1.56 [1.27–1.90]	**<0.0001**
pT of the primary tumor (pT_{1-2} vs pT_{3-4})	1.25 [1.06–1.48]	**0.007**
Lymph node involvement of the primary tumor (pN_0 vs pN_{1-2})	2.12 [1.49–3.03]	**<0.0001**
Preoperative CRP serum levels > 0.6 mg/dL	1.55 [1.09–2.20]	**0.014**
Preoperative VO_2max <17 mL/min/kg	1.42 [1.02–2.00]	**0.040**

Notes: Cox proportional hazard regression analysis assessing the independent predictors of survival in patients with operable lung cancer stratified by COPD severity. Significant p-values are in bold.
Abbreviations: COPD, chronic obstructive pulmonary disease; pT, Tumor stage of the intraoperative specimen according to TNM7 classification of primary lung tumors;[19] CRP, C-reactive protein; VO_2 max, maximum rate of oxygen consumption during physical exertion; Exp (B), Hazard ratio, 95% Confidence interval [lower bound-upper bound].

53.7% in Group 2). No significant differences in the distribution of histological subtypes and differentiation grades of the primary tumor were observed between groups.

The characteristics of the surgical approach were summarized in Table 4. In the majority of cases, an open surgical approach was performed (64.3% in Group 1 and 55.2% in Group 2). Conversion to open surgery was required in 11.0% of patients in Group 1 and 13.4% in Group 2. Regarding the extent of the surgical procedure, Group 2 patients underwent more frequently segmentectomies in comparison to Group 1 patients (3.9% vs 16.4%, p<0.001).

Independent of COPD severity, surgery time was comparable between groups, with a median surgery time of 182.00 [145.25; 220.00] minutes in Group 1 and 187.50 [142.25; 225.50] minutes in Group 2. Similarly, median blood loss was 400 [300.00; 500.00] mL in both groups, with no significant differences reported (p=0.423, Table 4).

Perioperative Morbidity and Mortality

The perioperative patient care was comparable between groups. The cumulative volume of the pleural fluid drained via chest tubes was not significantly different between groups (median volume 1930.00 [1250.00; 2800.00] mL). The chest tube was removed after 6 [5.00; 8.00] days. Mortality during follow-up was significantly higher in Group 2 (61.2% vs 45%, p=0.0014). A detailed description of postoperative morbidity and mortality is provided in Table 5.

Group 2 patients experienced a higher frequency of prolonged air leaks (>5 days, 8.7% in Group 1 and 17.9% in Group 2, p=0.020). The most common postoperative complications were pneumonia (16.1% in Group 1 and 26.9% in Group 2, p=0.032), prolonged invasive ventilation (>2 days, 3.7% in Group 1 and 10.4% in Group 2, p=0.016), arrhythmias (8.2% in Group 1 and 17.9% in Group 2, p=0.012) and secondary wound infections (1.2% in Group 1 and 4.5% in Group 2, p=0.057, Table 5). Consecutively, the in-hospital stay in Group 2 patients was significantly longer when compared to Group 1 patients (15.0 [12.0; 20.0] days in Group 1 vs 18.0 [15.0; 27.0] days in Group 2, p=0.0004, Table 5).

Univariate Analysis of Risk Factors

Overall Survival

Overall, 225 death events were reported during 1955 follow-up years. The median overall survival (OS) for the entire cohort was 75.5 [62.7–88.2] months (Figure 2A).

Patients aged 65 years or older had a significantly decreased OS compared to younger patients (5-year OS: 52.6% vs 62.8%, p=0.002). Male patients had a significantly worse prognosis compared to female patients (5-year OS: 52.4% vs 63.4%, p=0.023).

Patients with COPD III–IV had a significantly decreased OS in comparison to patients with COPD I–II (5-year OS: 44.0% vs 59.0%, p=0.001, Figure 2B). Correspondingly, mortality was significantly higher in patients with COPD III–IV in comparison to COPD I–II patients (61.2% vs 45.0%, p=0.014, Table 5).

Patients with the following comorbidities experienced significantly decreased OS compared to those without: lung fibrosis (5-year OS: 12.5% vs 57.8%, p<0.001), arterial hypertension (5-year OS: 51.6% vs 63.1%, p=0.020), ischemic heart disease (5-year OS: 44.5% vs 58.8%, p=0.046), peripheral arterial disease (5-year OS: 37.7% vs 59.0%, p=0.006), and moderate-severe kidney insufficiency (5-year OS: 51.0% vs 56.9%, p=0.044). Reflecting the multimorbidity of patients with lung cancer and COPD, an ASA score >2 and a CCI>2 were associated with decreased OS (5-year OS for ASA score >2: 55.1% vs 67.4%, p=0.010 and 5-year OS for CCI>2: 54.4% vs 65.9%, p=0.014, respectively).

Laboratory parameter associated with decreased OS included: serum CRP>0.6 mg/dL (5-year OS: 44.8% vs 69.2%, p<0.001, Figure 2C), albumin<3.75 mg/dL (5-year OS: 49.2% vs 64.8%, p=0.015) and creatinine>1.2 mg/dL (5-year OS: 45.4% vs 60.6%, p=0.005). A serum CYFRA 21–1 level >1.96 ng/mL was associated with decreased OS (5-year OS: 50.9% vs 64.2%, p=0.003). Patients with VO_2max>17 mL/min/kg had a better prognosis compared to those with lower VO_2max values (5-year OS: 61.2% vs 51.1%, p = 0.025, Figure 2D).

While topography of the primary tumor was not associated with OS, the following tumor characteristics were significantly linked to decreased OS: large tumors (5-year OS: pT_{3-4} 38.0% vs pT_{1-2} 61.6%, p<0.001, Figure 2E), lymph node involvement (5-year OS: pN_{1-2} 36.5% vs pN_0 66.5%, p<0.001, Figure 2F), presence of metastasis (5-year OS: M_0 58.3% vs $M_1$15.0%, p<0.001), non-adenocarcinoma histological subtypes (5-year OS: 60.4% vs 51.7%, p=0.046) and low differentiation grade (5-year OS: G_3 48.8% vs G_{1-2} 63.4%, p = 0.010). Patients undergoing open surgery had significantly worse OS compared to those treated with minimally invasive techniques (5-year OS: open surgery 49.3% vs VATS 69.9%, p<0.001).

Patients experiencing major complications had significantly worse OS when compared to those patients without: acute thromboembolism (5-year OS: 0% vs 57.6%, p=0.001), hoarseness due to recurrent laryngeal nerve paralysis (5-year OS: 0.0% vs 57.7%, p<0.001), prolonged intubation (5-year OS: 30.7% vs 58.3%, p=0.003), re-intubation (5-year OS: 29.1% vs 58.7%, p<0.001) or tracheotomy (5-year OS: 0.0% vs 57.5%, p<0.001). Patients experiencing a postoperative local relapse (5-year OS: 31.6% vs 63.5%, p<0.001) or tumor progress (5-year OS: 27.6% vs 63.5%, p<0.001) demonstrated a significantly decreased OS.

Disease Free Survival (DFS)

We identified 77 tumor relapses (16.2%) in cumulatively 1812 years of follow-up. The mean DFS for the entire cohort was 134.94 [128.57–141.32] months (Figure 3A) and for patients experiencing tumor relapse 16.27 [12.77–19.78] months.

The 5-year DFS in patients with COPD III–IV was lower in comparison to the patients with COPD I–II (72.5% vs 81.2%, p=0.059, Figure 3B).

Preoperative laboratory (eg CRP>0.6 mg/dL, Figure 3C) and lung function parameters (eg VO_2max>17 mL/min/kg, Figure 3D) were not significantly associated with tumor relapse. Patients with serum CYFRA 21–1 levels >1.96 ng/mL had a significantly lower DFS when compared to those with lower CYFRA 21–1 levels (5-year DFS: 75.7% vs 82.5%, p=0.041).

Patients with large tumors ($pT_{3-4,}$ 5-year DFS 60.8%), lymph node involvement ($pN_{1-2,}$ 5-year DFS 64.8%), presence of metastasis ($M_{1,}$ 5-year DFS 45.8%) and low differentiated tumors (G_3, 5-year DFS 75.7%) had a significantly decreased DFS when compared to the patients with smaller tumors (pT_{1-2}, 5-year DFS 85.4%, p<0.001, Figure 3E), without nodal (5-year DFS 86.3%, p<0.001, Figure 3F) or extranodal metastatic disease (5-year DFS 80.9%, p=0.007) or high differentiated tumors (G_{1-2}, 5-year DFS 83.2%, p=0.035).

Anatomical resections were significantly linked to DFS (5-year DFS: lobar resections 82.4% vs multilobar resections 67.5%, p=0.003). Among postoperative complications, hoarseness due to recurrent laryngeal nerve paralysis was the only complication significantly associated with decreased DFS (5-year DFS: 0.0% vs 80.5%, p=0.018).

Multivariable Analysis of Risk Factors

Multivariable Cox regression analysis identified the following parameters as independent negative predictors of long-term OS: COPD III–IV (Group 2), large tumors (pT_{3-4}), hilar or mediastinal lymph node involvement (pN_{1-2}), as well as elevated serum CRP levels (>0.6 mg/dL) and decreased VO_2max<17 mL/min/kg (Figure 4A, B and Table 6). These predictors increased the risk of death by 1.6-, 1.3-, 2.1-, 1.6-, and 1.4-fold, respectively (Figure 4A, B and Table 6). These results were reproduced using three selection methods (Enter, Forward LR and Backward LR) and further validated using decision tree analyses with two independent algorithms (CRT, QUEST, Figure 4C). Accordingly, COPD severity showed a significant role in patients with normal CRP levels (<0.6 mg/dL) and no lymph node involvement (pN_0, Figure 4C). The regression model is summarized in Table 6.

The robustness of the abovementioned predictors was further analyzed in relation to clinically relevant confounders, previously insufficiently characterized in combination with COPD severity, TNM staging, lung function, and laboratory parameters. When considering age >65 years, sex, BMI, nicotine consumption, histology, operative approach and surgical extent as potential confounders, the multivariable analysis showed qualitatively unchanged results (Supplementary Table S1). Importantly, these results were validated through two multivariable models, demonstrating robustness and consistency in our findings.

Disscusion

The aim of the study was to comprehensively characterize a cohort of patients with operable lung cancer and varying COPD grades to identify independent predictors of reduced long-term overall survival (OS) and optimize preoperative risk stratification and patient care. This study was conducted in a high-volume thoracic surgery clinic comprising 1663 operable lung cancer patients with co-occurring COPD (28.6%) in line with previous reports.[23–25] The distribution of COPD grades (I/II/III/IV-31.3%/ 54.6%/13.9%/0.2%) was in line with previous findings (I/II/III-50.6%/42.0%/7.4%[25]). This concordance demonstrates the validity of our results and allows for further considerations.

The present study specifically analyzed well-established clinical parameters including preoperative laboratory and lung function tests, comorbidities, as well as radiological, histological tumor and surgical characteristics, in relation to short and long-term postoperative outcomes. Accordingly, the univariate analysis stratifying patients into two COPD severity groups, showed no significant differences in laboratory parameters, BMI, smoking history or associated comorbidities. These findings are consistent with previous studies, reporting that the coexistence of COPD in lung cancer patients was independent of factors such as age, sex and smoking history.[3,24]

No significant differences were observed in our study regarding the topography, TNM classification, histological subtypes and differentiation grades of the primary tumors. These findings are consistent with previous studies, reporting no significant correlation between COPD severity and TNM stage. This suggests that lung function alterations do not directly influence tumor size, lymph node involvement, or metastasis.[6] Regarding the relationship between histological subtypes and COPD severity, prior studies have reported contradictory results. While some studies observed an increased frequency of squamous cell carcinoma in COPD patients,[26–28] others found no specific histological correlation with COPD.[29]

Although no association between surgical approaches (open vs minimally invasive) and COPD severity was observed, COPD III–IV patients underwent more frequently segmentectomies. These results align with previous studies addressing the outcomes of the surgical approach,[30,31] and the increased frequency of segmentectomies in patients with compromised lung function.[32] Although segmentectomy has been proposed as a feasible treatment option for patients with impaired lung function, limited data are available addressing this approach in patients with varying COPD grades. Our study shows that the increased frequency of segmentectomies in COPD III–IV patients reflect their significantly reduced lung function (Table 1) and clinical condition, in line with existing evidence supporting sublobar resections in high-risk patients.[30,33–35] Accordingly, Yang et al found comparable survival probabilities for patients undergoing segmentectomies, when compared to those undergoing lobectomies.[32]

Reflecting functional and radio-morphological alterations (eg air trapping, incomplete fissures), patients suffering from severe COPD experienced more frequently a prolonged air leak, as well as respiratory and cardiac complications, further validating adverse postoperative events reported in other surgical cohorts.[8,25]

The abovementioned parameters were incorporated in a survival analysis considering COPD severity and relevant clinical confounders. This analysis identified serum levels of CRP>0.6 mg/dL, albumin>3.75 g/dL, creatinine>1.2 mg/dL and CYFRA 21–1>1.96 ng/mL as significant risk factors for a decreased OS. These associations were in line with previous studies, showing worse outcomes in lung cancer patients with elevated inflammatory parameters (>0.4 mg/dL[36]), impaired kidney function (creatinine>1.2 mg/dL[37,38]) or increased tumor markers (CYFRA 21–1>4.18 ng/mL[39]).

Similarly, our study identified a VO_2 max<17 mL/min/kg as significant factor for reduced OS in accordance with prior findings (VO_2max<12 mL/min/kg[40] or <15 mL/min/kg[41]).

Additional clinical parameters associated with worse OS included male sex, age >65 years and the presence of comorbidities such as respiratory diseases (eg lung fibrosis), cardiovascular conditions (eg arterial hypertension, ischemic heart disease), peripheral vascular disease and severe chronic kidney disease.[42–46] These widely documented associations suggest that lung cancer patients with COPD often experience a higher burden of comorbidities, negatively affecting survival. In line with this comorbidity profile, an ASA>2 and a CCI>2 were also identified as risk factors for reduced survival in our study. Although these associations are well-established in broader patient populations, there are no studies addressing all these risk factors together in lung cancer patients with varying COPD grades, making our findings particularly valuable.

In line with studies reporting the non-inferiority of minimally invasive procedures compared to open approaches in patients with operable lung cancer,[47–49] our study specifically demonstrated a survival benefit upon minimally invasive procedures in the subgroup of lung cancer patients with COPD. This particular aspect of our study underlines the importance of less invasive and painful surgical approaches in patients with relevant comorbidities and impaired lung function.

Consistent with previous studies, large tumors ($pT_{3\text{-}4}$), lymph node involvement ($pN_{1\text{-}2}$), presence of metastasis (M_1), non-adenocarcinoma histology, a low differentiation grade (G_3) and local tumor relapse were associated with worse survival outcomes.[50–53] Moreover, acute thromboembolism and prolonged mechanical ventilation were confirmed as negative predictors of OS, aligning with previous findings[54–56] in patients with associated respiratory[45] and cardiac comorbidities.[57]

The abovementioned OS probabilities were in line with significantly reduced DFS estimates in patients experiencing elevated CYFRA 21–1 levels, large tumors ($pT_{3\text{-}4}$), lymph node involvement ($pN_{1\text{-}2}$), metastasis (M_1) or a low tumor differentiation grade (G_3). Patients undergoing lobar resections showed an improved DFS compared to those undergoing multilobar resections, highlighting the critical role of parenchymal sparing surgery in patients with compromised lung function.[14,15,58]

The clinically meaningful parameters that were found to be significant in the univariate survival analysis were included in the multivariable Cox regression analysis to show their independent predictive value. This analysis revealed COPD III–IV, $pT_{3\text{-}4}$, $pN_{1\text{-}2}$ as well as CRP>0.6 mg/dL and VO_2max<17 mL/min/kg as significant independent predictors of worse long-term OS, increasing the risk of death by 1.6-, 1.3-, 2.1-, 1.6-, and 1.4-fold, respectively. These findings provide additional value in comparison to previous reports identifying only COPD severity and tumor growth as independent predictors of OS in lung cancer patients.[50,59–61]

Notably, these predictors and confounders represent clinically established parameters that are routinely collected on hospital admission in most Thoracic Surgery, Pneumology and Oncology departments. Their routine availability underscores their potential usefulness as practical tools for preoperative risk assessment and patient selection for surgical treatment.[14]

From a clinical point of view, COPD is a progressive, irreversible and life-threatening disease that significantly worsens the prognosis of lung cancer patients. Beyond increasing the risk of lung cancer (4-to 6-fold higher, with an annual incidence of 0.8–1.7%[1,27,29–31]), COPD contributes to tumor progression through mechanisms such as chronic inflammation, immunosuppression, oxidative stress, tissue remodeling, epithelial to mesenchymal transition, and smoking-related tissue damage.[2,4,62,63] As a result, the co-occurrence of COPD in lung cancer patients represent a challenge in the perioperative patient management resulting in higher morbidity and mortality. Our results are consistent with previous studies and confirm that COPD patients have an increased risk of developing postoperative complications such as pneumonia, prolonged medical ventilation,[45] and cardiovascular events.[43] These risks emphasize the need for a rigorous preoperative cardiopulmonary and radiological evaluation, to determine the optimal extent of the surgical procedure.

The strength of our study lies in its comprehensive comparative analysis of a large cohort of patients with operable NSCLC and varying COPD severity. This aspect is particularly relevant, given the increasing prevalence of environmental and cigarette smoke exposure as major contributors to both COPD and lung cancer. Unlike previous studies primarily addressing patients with mild/moderate obstruction, our cohort includes a representative subgroup of patients with severe COPD, and thus provides valuable insights into an underrepresented patient cohort previously insufficiently characterized. This is of particular interest in the preoperative risk stratification and assessment of surgical eligibility.

Notably, our study observed a higher frequency of segmentectomies in COPD III–IV patients, highlighting the importance of adopting individualized, less invasive surgical approaches for patients with relevant comorbidities and severely impaired lung function.

Moreover, identifying high-risk patients may help in selecting candidates for preoperative rehabilitation programs designed to improve preoperative lung function and patient condition.[11,14,64,65] These aspects are particularly relevant to assess the appropriate extent of surgery as well as improve postoperative outcomes.

The present study has several limitations. First, due to the retrospective nature of the manuscript, which included patients from 2011 to 2020, it was not always possible to collect complete data for all patients or prospectively assess variables for the specific purpose of this study. However, missing data were found to be <10% for the majority of the selected variables, thus reducing the likelihood for non-significant results. One exception was VO2max, since assessment of the cardiopulmonary condition was performed according to ESTS Guidelines only in patients with impaired lung function (FEV1 or DLCO<60%). When excluding VO2max from the analysis, the cox proportional hazard model turned out qualitatively unchanged results validated by three selection methods (Enter, Forward LR and Backward LR).

Second, the number of patients with severe COPD limited the multivariable regression analysis to a maximum of six variables, selected based on clinical relevance.

Conclusions

In summary, this study performed a comprehensive descriptive analysis of operable lung cancer patients with varying COPD grades, and identified a panel of clinically meaningful parameters significantly associated with COPD severity and long-term survival. These predictors may help in preoperative risk stratification and assessment of surgical extent, particularly given the increased postoperative morbidity and mortality observed in lung cancer patients with COPD. For future research, we recommend validating our results in multicenter randomized controlled trials to consolidate the findings.

Abbreviations

ARDS, acute respiratory distress syndrome; ASA, American Society of Anesthesiologists; BMI, body mass index; CEA, carcinoembryonic antigen; CCI, Charlson Comorbidity Index; CIs, confidence intervals; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease; CRT, Classification and Regression Trees; CYFRA 21-1, cytokeratin fraction 21–1; DFS, disease-free survival; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in one second; GOLD, Global Initiative for Obstructive Lung Disease; HRs, Hazard ratio; ICU, Intensive care unit; IQRs, interquartile range; LDH, lactate dehydrogenase; LMU, Ludwig-Maximilians-University of Munich; LR, Likelihood Ratio; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; NSE, neuron specific enolase; OS, overall survival; pM, Metastasis of the intraoperative specimen; pN, Lymph node status of the intraoperative specimen; proGRP, pro-gastrin-releasing peptide; pT, Tumor stage of the intraoperative specimen; PY, pack-years; QUEST, Quick, Unbiased, 205 Efficient Statistical Tree; RNL, recurrent laryngeal nerve;; ROC, receiver-operator characteristics; TIA, transient ischemic attack; TNM, Tumor node metastasis staging system; VATS, video-assisted thoracoscopic surgery; VC, vital capacity; VO2max, maximum oxygen consumption during physical exertion; UICC, The Union for International Cancer 157 Control; WHO, World Health Organization; ROC, receiver operating characteristics.

Data Sharing Statement

The datasets of the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Approval for this retrospective, non-interventional study was obtained from the Ethics Committee of the Ludwig-Maximilian's University Munich (LMU), Germany (reference number 21-0036). This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local ethical and legal requirements. A database with the parameters collected was created for the study. The names of the patients and all other confidential information are subject to medical confidentiality and the provisions of the Federal Data Protection Act (BDSG). Personal data and findings about the patient were collected, stored, encrypted (pseudonymized) and stored in the shared database at the University of Ludwig Maximilian University. The administration of the data was carried out by the applicant or study director as the person responsible for the study. The need for written informed consent was waived by the above-mentioned ethics committee due to retrospective nature of the study.

Acknowledgments

We thank all colleagues from the Asklepios Lung Clinic Gauting, Germany, Departments of Thoracic Surgery, Radiology, Pneumology and Pathology for excellent clinical patient care, clinical expertise and support in the data collection.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

Prof. Dr. Niels Reinmuth reports personal fees from Amgen, personal fees from Astra Zeneca, personal fees from Bristol-Myers Squibb, personal fees from Boehringer-Ingelheim, personal fees from Daiichi-Sankyo, personal fees from GlaxoSmithKline, personal fees from Hoffmann-La Roche, personal fees from Janssen, personal fees from Lilly, personal fees from MSD, personal fees from Pfizer, personal fees from Sanofi, personal fees from Takeda, outside the submitted work. The authors declare no conflict of interest.

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