Original Study

Comorbidity in Patients With Small-Cell Lung Cancer: Trends and Prognostic Impact

Mieke J. Aarts,[1] Joachim G. Aerts,[2,3] Ben E. van den Borne,[4] Bonne Biesma,[5] Valery E.P.P. Lemmens,[1,6] Jeroen S. Kloover[7]

Abstract

The present study is the first on the trends in comorbidity among patients with small-cell lung cancer. In particular, hypertension and pulmonary, cardiac, and vascular disease have become more common. Multimorbidity and cardiac and digestive disease have affected survival in those with limited-stage disease, and cardiac and cerebrovascular disease have decreased the survival of patients with extensive disease. These data are relevant for treatment decisions and patient communication in daily clinical practice.

Introduction: We evaluated the trends in the prevalence of comorbidity and its prognostic impact in a cohort of unselected patients with small-cell lung cancer (SCLC). **Patients and Methods:** All patients (n = 4142) diagnosed with SCLC from 1995 to 2012 were identified from the population-based Netherlands Cancer Registry in the Eindhoven region. **Results:** The prevalence of comorbidity increased from 55% in 1995 to 1998 to 76% in 2011 to 2012 and multimorbidity (ie, ≥ 2 concomitant diseases) from 23% to 51%. The prevalence of a comorbidity increased with age. Among the men, hypertension, cardiac disease, and diabetes, in particular, became more common (increased from 11% to 35%, from 19% to 36%, and from 7% to 18%, respectively). In the women, the rate of pulmonary disease, hypertension, and cardiac disease increased the most (increased from 18% to 30%, from 12% to 28%, and from 11% to 24%, respectively). Multimorbidity was associated with a slightly increased hazard of death, independent of treatment in those with limited-stage SCLC (hazard ratio [HR] for ≥ 2 comorbidities vs. no comorbidities, 1.2; 95% confidence interval [CI], 1.0-1.4). The prognostic effects of multimorbidity resulted from treatment in those with extensive-stage SCLC (HR for ≥ 2 comorbidities vs. no comorbidities, final model, 1.2; 95% CI, 1.0-1.2). The prognostic impact of the specific comorbidities varied, with digestive disease reducing the hazard and cardiac disease increasing the hazard in those with limited-stage SCLC (HR for digestive disease vs. no digestive disease, 0.7 [95% CI, 0.5-0.9], and HR for cardiac vs. no cardiac disease, 1.2 [95% CI, 1.0-1.3]). Also, cardiac and cerebrovascular disease increased the hazard in those with extensive-stage SCLC (HR 1.2 [95% CI, 1.0-1.3] and HR 1.3 [95% CI, 1.1-1.6], respectively). **Conclusion:** Comorbidity among patients with SCLC is very common and has been increasing. Multimorbidity was associated with a slightly increased hazard of death in those with limited-stage SCLC, independent of treatment. However, the prognostic effects in those with advanced-stage SCLC resulted from treatment. Digestive disease favorably affected survival and cardiac disease negatively affected the prognosis for those with limited-stage SCLC, and cardiac and cerebrovascular diseases had a negative prognostic effect for those with extensive-stage SCLC. With the burden of comorbidities in patients with SCLC increasing, more attention to individualized treatment approaches is needed.

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[1]Netherlands Cancer Registry, Netherlands Comprehensive Cancer Organisation (IKNL), Eindhoven, The Netherlands
[2]Department of Pulmonary Diseases, Amphia Hospital, Breda, The Netherlands
[3]Department of Pulmonary Diseases, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands
[4]Department of Pulmonary Diseases, Catharina Hospital, Eindhoven, The Netherlands
[5]Department of Pulmonary Diseases, Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands
[6]Department of Public Health, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands
[7]Department of Pulmonary Diseases, TweeSteden Hospital and St. Elisabeth Hospital, Tilburg, The Netherlands

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Address for correspondence: Mieke J. Aarts, PhD, Netherlands Cancer Registry, Netherlands Comprehensive Cancer Organisation (IKNL), PO Box 231, Eindhoven 5600 AE, The Netherlands
E-mail contact: m.aarts@iknl.nl

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Introduction

Worldwide, lung cancer is the most common cancer in men (1.2 million cases annually) and the fourth most common cancer among women (583,000 cases annually).[1] It is the leading cause of death from cancer. Lung cancer is commonly classified as small-cell lung carcinoma (SCLC) and non–small-cell lung carcinoma (NSCLC). SCLC is a highly aggressive neoplasm and is often diagnosed in the presence of other chronic medical conditions. These comorbidities can complicate the therapeutic options because of, among others, decreased life expectancy, interactions between the comorbidity and the cancer therapy, polypharmacy, and, in the elderly, age-related physiologic changes.[2] The presence of a comorbidity was associated with less aggressive treatment or abstaining from treatment in patients with SCLC.[3] Whether the presence of a comorbidity also affects the prognosis of patients with SCLC is not yet clear, because both negative prognostic effects and the absence of an effect have been reported.[3-5]

The presence of a comorbidity in patients with cancer has not only been associated with increasing age, but also with sex and socioeconomic status.[5-7] Furthermore, the prevalence of a comorbidity could change over time owing to the aging of patients, improved life expectancy, and changing lifestyle habits. Monitoring the presence of comorbidities will improve the awareness of the effect of these diseases, among both clinicians and researchers. However, data on the trends in the prevalence of comorbidities in patients with SCLC are scarce.

In the present study, we evaluated the trends in the prevalence of comorbidities in a large cohort of unselected patients with SCLC during an 18-year study period. We also studied the prognostic effect of comorbidities in these patients and investigated whether these effects resulted from differences in treatment.

Materials and Methods

All patients newly diagnosed with SCLC from 1995 to 2012 in the Eindhoven region of the population-based Netherlands Cancer Registry were included. The Cancer Registry in the Eindhoven region records the data from all patients with cancer in the southern Netherlands, an area with approximately 2.4 million inhabitants (about 15% of the Dutch population) and no academic hospitals. Trained registry personnel actively collected data from the medical records on the patient characteristics, such as sex, birth date, postal code, and comorbidities, and the tumor characteristics, such as the date of diagnosis, tumor type, subsite ("International Classification of Diseases for Oncology"),[8] histologic type, tumor grade, and initial treatment. The stage was recorded according to the TNM classification[9] and the system developed by the Veterans Administration Lung Cancer Study Group (VALSG). In the present study, we classified the tumors as limited (tumor confined to 1 hemithorax, including the contralateral hilus lymph nodes, mediastinum, ipsilateral supraclavicular lymph nodes, and metastases to the ipsilateral lung) and extensive (all other tumors and, among other factors, distant metastases, except for metastases to the ipsilateral lung). This staging was primarily referenced using the VALSG classification and supplemented with the clinical TNM stage (N3 and M1 were classified as extensive and M0 as limited). The quality of the cancer registry data is high owing to thorough training of the registration clerks and a variety of computerized consistency checks at the regional and national levels. Completeness has been estimated to be $\geq$ 95%.[10] Information on the vital status of the patients was obtained from the population registries network, which provides virtually complete coverage of all deceased citizens of The Netherlands. The follow-up data were complete until January 1, 2014. We included all patients diagnosed at 1 of the 10 hospitals in the Eindhoven region.

Socioeconomic status, determined from the individual fiscal data on the economic value of the home and household income, was provided at an aggregated level for each postal code.[11] The socioeconomic status was categorized into tertiles. A separate class was used for postal codes in areas with a long-term care-providing institution.

Treatment was classified as surgery with or without adjuvant therapy (for limited disease), chemotherapy plus radiotherapy, chemotherapy alone, no therapy, prophylactic cranial irradiation, and other (including radiotherapy to the primary tumor, metastasis-directed therapy, and other).

Since 1993, information on the presence of comorbidities was routinely collected for the Eindhoven region of the Netherlands Cancer Registry by screening the patients' previous admissions, letters of referral from and discharge to general practitioners, the

Table 1 Disease Categories for Comorbidity Registered by The Netherlands Cancer Registry in the Eindhoven Region

Disease Category	Comorbid Conditions
Other malignancy	Other malignancy; excluded: basal cell carcinoma and carcinoma in situ of the cervix
Pulmonary disease	Obstructive and restrictive pulmonary disease, lung fibrosis, lung transplantation
Cardiac disease	Myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty of the heart, heart decompensation, angina pectoris, heart valve disease, heart failure, heart transplantation, heart rhythm disorder, pericarditis, cardiomyopathy, pacemaker
Vascular disease	(Deep venous) thrombosis, lung embolus, generalized arterial atherosclerosis, peripheral arterial disease, percutaneous transluminal angioplasty, abdominal aneurysm, abdominal aortic surgery
Cerebrovascular disease	Cerebrovascular accident, hemiplegia, hemiparesis, quadriplegia, carotid surgery (TIA excluded)
Hypertension	Systemic hypertension, portal hypertension
Diabetes mellitus	Insulin dependent, oral medication dependent, diet dependent
Infectious disease	HIV, AIDS, tuberculosis
Digestive tract disease	Ulcer disease, reflux esophagitis, (partial) stomach resection, chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis, inflammatory bowel disease), liver disease, liver transplantation, diverticulitis. Excluded: polyposis coli
Genitourinary disease	Chronic glomerulonephritis, kidney failure, nephrotic syndrome, kidney transplantation, dialysis, pregnant at diagnosis
Muscle, connective tissue and joint disease	Connective tissue disease, sarcoidosis, Wegener's disease, polyarteritis nodosa, systematic lupus erythematosus, rheumatoid arthritis
Central and peripheral nervous system	Dementia, Alzheimer's disease, Parkinson disease, serious psychiatric disease (severe depression, admittance to a psychiatric unit, psychosis, schizophrenia)

Abbreviations: AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus; TIA = transient ischemic attack.

medical history, current medication usage, and preoperative assessments.[12-14] Internal validation studies were performed to evaluate the data quality by checking the completeness and accuracy of the registry personnel extracting the comorbidity information from the medical records in random cases.[15] Comorbid diseases were defined as life-shortening diseases present at the SCLC diagnosis. If ≥ 2 chronic conditions coexisted in ≥ 2 organ systems, this was referred to as multimorbidity. For the classification of comorbidity, we used a slight modification of the Charlson comorbidity index[12] to categorize comorbidity (Table 1).

The prevalence of the comorbidities was analyzed according to age, sex, period, and socioeconomic status. For the analyses of the time trends, we defined 5 periods: 1995 to 1998, 1999 to 2002, 2003 to 2006, 2007 to 2010, and 2011 to 2012. Patient age at the

Table 2 General Patient Characteristics and Percentage of Patients With Comorbidity Stratified by Age, Sex, and Socioeconomic Status

Variable	1995-1998	1999-2002	2003-2006	2007-2010	2011-2012	Relative Change[a]	Total	*P* Value
General characteristic								
Patients (n)	876	811	926	1019	510		4142	
Sex								
Male	72%	69%	61%	59%	51%	0.71	63%	<.0001[b]
Female	28%	31%	39%	41%	49%	1.75	37%	
Age								
Mean (years)	65.0	65.9	65.9	66.4	67.8	1.04	66.1	<.0001[c]
0-59	26%	26%	26%	24%	19%	0.74	25%	.0106[d]
60-69	40%	35%	36%	35%	37%	0.93	37%	
70-79	29%	33%	32%	33%	34%	1.18	32%	
≥80	6%	6%	6%	7%	10%	1.75	7%	
Socioeconomic status								
Low	37%	35%	33%	32%	33%	0.88	34%	<.0001[d]
Intermediate	40%	39%	42%	38%	37%	0.94	40%	
High	18%	22%	20%	24%	22%	1.23	21%	
Institutionalized	4%	4%	3%	3%	2%	0.46	3%	
Unknown	1%	1%	1%	3%	6%	8.37	2%	
Comorbidity prevalence								*P* Value Trend[b]
Overall								
≥1 Comorbidities	55%	64%	65%	72%	76%	1.39	66%	<.0001
≥2 Comorbidities	23%	34%	37%	40%	51%	2.21	36%	<.0001
Unknown	7%	8%	9%	3%	2%	0.22	6%	<.0001
Prevalence of ≥1 comorbidities								
Sex								
Male	59%	67%	67%	73%	80%	1.37	68%	<.0001
Female	45%	60%	61%	70%	72%	1.59	62%	<.0001
Age (years)								
0-59	33%	44%	45%	51%	56%	1.70	45%	<.0001
60-69	58%	64%	64%	73%	71%	1.21	66%	<.0001
70-79	69%	79%	78%	83%	88%	1.28	79%	<.0001
≥80	61%	72%	83%	86%	96%	1.57	80%	<.0001
Socioeconomic status								
Low	60%	71%	70%	74%	78%	1.29	70%	<.0001
Intermediate	53%	63%	63%	71%	75%	1.42	64%	<.0001
High	46%	60%	57%	69%	75%	1.63	61%	<.0001
Institutionalized	68%	55%	70%	85%	90%	1.33	70%	.03
Unknown	50%	60%	67%	73%	76%	1.52	71%	.2

[a]Relative relative difference between the prevalence in 1995-1998 and 2011-2012.
[b]Two-sided Cochran Armitage trend test.
[c]*t* Test for last versus first period.
[d]χ^2 test.

diagnosis of cancer was grouped as follows: < 60, 60 to 69, 70 to 79, and ≥ 80 years. To evaluate the comorbidity changes over time, the prevalence of a comorbidity was estimated as a percentage per a 4-year period and analyzed for the different age groups, sex, and socioeconomic status. A χ^2 test was used to analyze the categorical variables, a Cochran-Armitage trend test was used for trends among the dichotomous variables, and a *t* test was used to compare the mean age between 2 periods. Multivariable logistic regression analysis was conducted for the following determinants of comorbidity: age, sex, socioeconomic status, and year of diagnosis. The survival time was defined as the interval from diagnosis to the date of death or January 1, 2014 for patients still living. A multivariable proportional hazards regression analysis was used to discriminate the independent risk factors for death. The models were stratified according to stage (data for unknown stage not shown, n = 409, 10%) and adjusted for sex, age, socioeconomic status, year of diagnosis, and comorbidity (model A). To evaluate the prognostic effect of a specific comorbidity, a separate model for each concomitant disease was constructed (eg, hypertension vs. no hypertension) without adjustment for the number of comorbidities or other specific concomitant diseases. To evaluate whether the comorbidity affected survival because of the therapy received, a separate model was built that included the therapy (model A plus therapy = model B). The analyses were performed using SAS, version 9.3 (SAS Institute, Cary, NC). The *P* values were 2-sided, and *2P* < .05 was considered significant.

Results

Patient Characteristics

A total of 4142 patients was diagnosed with primary invasive SCLC from 1995 to 2012 and included for analysis. The median age was 67 years. The mean age of all patients with SCLC increased slightly from 65.0 to 67.8 years during the study period (Table 2). Most of the patients were male (63%), although the proportion of women increased from 28% to 49%. Of the 4142 patients, 66% had ≥ 1 comorbid disease. Multimorbidity was present in 36% of the patients with SCLC. The men suffered more from comorbidities than the women (68% vs. 62%). Also, patients with a low socioeconomic status had concomitant disease more often than did those with a high socioeconomic status (70% vs. 61%). With increasing age, the prevalence of comorbidities increased: 45% of the patients < 60 years had a comorbidity compared with 80% of those > 80 years.

Trends in Comorbidity Prevalence

The prevalence of comorbidities increased from 55% in 1995 to 1998% to 76% in 2011 to 2012, and the prevalence of multimorbidity increased from 23% to 51% (Table 2). This trend was observed in all age groups, most strongly for those aged ≤ 59 years and those aged ≥ 80 years. During the study period, the increase in the prevalence of comorbidities was strongest in women, with a relative difference of 1.59 between the prevalence in 1995 to 1998 and 2011 to 2012.

Table 3 Multivariable Odds of Comorbidity or Multimorbidity for Patients With Small Cell Lung Cancer in the Southern Netherlands, 1995-2012

	≥1 Comorbidities		≥2 Comorbidities	
Variable	**OR[a]**	**95% CI**	**OR[a]**	**95% CI**
Diagnostic period				
1995-1998	1.0		1.0	
1999-2002	1.5[b]	1.2-1.9	1.8[b]	1.4-2.2
2003-2006	1.6[b]	1.3-1.9	2.0[b]	1.6-2.5
2007-2010	2.2[b]	1.8-2.7	2.4[b]	1.9-2.9
2011-2012	2.7[b]	2.1-3.4	3.6[b]	2.8-4.6
Sex				
Male	1.0		1.0	
Female	0.9[b]	0.7-1.0	0.7[b]	0.6-0.9
Age (years)				
≤59	1.0		1.0	
60-69	2.3[b]	1.9-2.7	2.6[b]	2.1-3.2
70-79	4.4[b]	3.6-5.3	4.5[b]	3.7-5.5
≥80	4.5[b]	3.2-6.2	5.6[b]	4.1-7.5
Socioeconomic status				
Low	1.5[b]	1.2-1.8	1.5[b]	1.2-1.8
Intermediate	1.2	1.0-1.4	1.3[b]	1.1-1.6
High	1.0		1.0	
Institutionalized	1.4	0.9-2.1	1.5[b]	1.0-2.3
Unknown	1.1	0.7-1.9	1.9[b]	1.2-3.1

Abbreviations: CI = confidence interval; OR = odds ratio.
[a]Adjusted for all variables listed.
[b]Statistically significant.

The increasing trend remained significant after multivariable adjustment. The odds ratio (OR) of having any comorbidity or multimorbidity was 2.7 (95% confidence interval [CI], 2.1-3.4) and 3.6 (95% CI, 2.8-4.6), respectively, for the last versus the first period (2011-2012 vs. 1995-1998; Table 3). Furthermore, increasing age, male sex, a low socioeconomic status, and institutional living were associated with an increased risk of having ≥ 1 concomitant diseases (OR for age ≥ 80 vs. ≤ 59, 4.5 [95% CI, 3.2-6.2]; OR for female vs. male gender, 0.9 [95% CI, 0.7-1.0]; and OR for low vs. high socioeconomic status, 1.5 [95% CI, 1.2-1.8]). The odds of having ≥ 2 comorbidities were slightly stronger in association with these factors.

Prevalence of Specific Comorbid Diseases Stratified by Age

The prevalence of all types of comorbidities increased with patient age. Pulmonary disease was the most common concomitant disease in patients aged ≤ 59 years (16%), followed by hypertension (12%) and cardiac disease (10%). The prevalence of cardiac disease increased strongly with age, being present in 40% of patients with SCLC aged ≥ 80 years. Pulmonary disease and hypertension was the second and third most common comorbid conditions in the oldest group at 33% and 26%, respectively.

Trends in Comorbidity Type Stratified by Sex

During the study period, the prevalence of comorbid diseases increased, except for pulmonary and digestive diseases in men and cerebrovascular accidents in both sexes (Table 4). Among the male patients, hypertension, cardiac disease, and diabetes mellitus became much more common (35%, 36%, and 18% in the last period, respectively), and pulmonary disease remained common but did not change significantly (ranging from 22% to 30%). Among the female patients, pulmonary disease remained the most prevalent comorbid disease, increasing from 18% to 30% in 2011 to 2012 (P value trend = .0003). Hypertension and cardiac and vascular diseases also became more common, present in 28%, 24%, and 14% of the patients with SCLC in the last period, respectively. Pulmonary disease, cardiac disease, and hypertension were the most common comorbidities in both men and women in 2011 to 2012, although men had the greatest prevalence of cardiac disease and women the greatest prevalence of pulmonary disease.

Effect of Comorbidities on Prognosis

The presence of multimorbidity affected crude survival in those with limited disease (1-year survival, 44% vs. 63% in patients without a comorbidity; log-rank, $P < .001$). To evaluate whether the presence of a comorbidity affected survival because of therapy, we constructed 2 multivariable models: 1 without (model A) and 1 with (model B) therapy. In the multivariable analyses, the presence of a comorbidity was not significantly related to survival (hazard ratio [HR] for ≥ 2 vs. no comorbidity, 1.1 [95% CI, 1.0-1.3]; Table 5, model A). However, the inclusion of therapy in the model (model B) led to a significant slightly increased hazard of death in patients with ≥ 2 comorbidities (HR, 1.2 [95% CI, 1.0-1.4]). More specifically, the presence of cardiac disease increased the hazard of death (HR, 1.2 [95% CI, 1.0-1.3]), but the presence of digestive disease reduced the hazard of death (HR, 0.7 [95% CI, 0.5-0.9]). The prognosis was most strongly affected by the therapy used, with an HR ranging from 0.5 for patients

Table 4 Percentage of Patients With Small-Cell Lung Cancer With Specific Comorbid Disease Stratified by Sex and Diagnostic Period, Southern Netherlands, 1995-2012

Variable	Diagnostic Period (%)					Average Change Annually (Abs %)	*P* Value Trend[a]
	1995-1998	1999-2002	2003-2006	2007-2010	2011-2012		
Men							
Diabetes mellitus	7	11	12	15	18	0.6	<.0001
Other malignancy	11	12	12	15	16	0.3	.0057
Pulmonary disease	22	24	23	24	30	0.4	.07
Cardiac disease	19	28	30	29	36	1.0	<.0001
Vascular disease	12	17	19	22	21	0.5	<.0001
Hypertension	11	16	18	26	35	1.4	<.0001
Cerebrovascular accident	4	5	5	6	7	0.1	.1
Digestive disease	7	10	6	6	9	0.1	.9
Women							
Diabetes mellitus	8	10	12	13	14	0.4	.0209
Other malignancy	10	10	11	14	16	0.3	.0162
Pulmonary disease	18	20	22	25	30	0.7	.0003
Cardiac disease	11	16	20	15	24	0.7	.0048
Vascular disease	4	11	10	19	14	0.6	<.0001
Hypertension	12	19	21	24	28	0.9	<.0001
Cerebrovascular accident	1	4	3	4	3	0.1	.2
Digestive disease	2	4	5	4	6	0.2	.03

Abbreviation: Abs % = absolute percentage difference.
[a]Two-sided *P* value using the Cochran-Armitage trend test.

Table 5 Crude and Multivariable Survival of Patients With Small-Cell Lung Cancer, Limited Stage, Southern Netherlands, 1995-2012

	Crude Survival		Multivariable Survival[a]			
			Model A		Model B	
Variable	1 year (%)	*P* Value[b]	HR[c]	95% CI	HR[c]	95% CI
Sex		<.01				
Male	49		1.0		1.0	
Female	57		0.9[d]	0.8-1.0	0.9[d]	0.8-1.0
Age (years)		<.001				
<60	66		1.0		1.0	
60-69	57		1.2[d]	1.1-1.5	1.1	1.0-1.3
70-79	42		1.8[d]	1.5-2.1	1.3[d]	1.1-1.5
≥80	17		4.2[d]	3.2-5.4	2.1[d]	1.6-2.7
Socioeconomic status		<.001				
Low	44		1.2[d]	1.0-1.4	1.2	1.0-1.4
Intermediate	56		1.0	0.9-1.2	1.0	0.9-1.2
High	60		1.0		1.0	
Institutionalized	39		1.2	0.8-1.7	1.3	0.9-1.9
Unknown	57		0.7	0.4-1.1	0.7	0.5-1.2
Diagnostic period		<.001				
1995-1998	49		1.0		1.0	
1999-2002	48		0.8[d]	0.7-1.0	0.9	0.8-1.1
2003-2006	53		0.8[d]	0.7-0.9	1.0	0.8-1.1
2007-2010	58		0.6[d]	0.5-0.7	0.8[d]	0.6-0.9
2011-2012	53		0.7[d]	0.5-0.8	1.0	0.8-1.3
Therapy						
Surgery ± Adj	78				0.6[d]	0.4-0.8
CT only	27				2.1[d]	1.8-2.4
None	6				5.6[d]	4.6-7.0
Other	70				1.4[d]	1.0-1.8
Prophylactic cranial RT	79				0.5[d]	0.4-0.7
RT + CT	70				1.0	
Comorbidities		<.001				
None	63		1.0		1.0	
1	53		1.0	0.9-1.2	1.1	0.9-1.2
≥2	44		1.1	1.0-1.3	1.2[d]	1.0-1.4
Unknown	43		1.5[d]	1.1-1.9	1.5[d]	1.1-1.9
Comorbidity type[e]						
Diabetes mellitus	47		1.2	1.0-1.4	1.2	1.0-1.4
Other malignancy	50		0.9	0.8-1.1	1.0	0.8-1.2
Pulmonary disease	44	<.01	1.1	1.0-1.3	1.1	1.0-1.3
Cardiac disease	41	<.001	1.2[d]	1.0-1.3	1.2[d]	1.0-1.3
Vascular disease	42	<.01	1.3[d]	1.1-1.5	1.2	1.0-1.4
Hypertension	48		1.0	0.9-1.2	1.0	0.9-1.2
Cerebrovascular disease	31	<.001	1.6[d]	1.2-2.2	1.3	0.9-1.7
Digestive disease	63		0.8	0.6-1.0	0.7[d]	0.5-0.9

Abbreviations: Adj = adjuvant therapy; CI = confidence interval; CT = chemotherapy; HR = hazard ratio; RT = radiotherapy.
[a]A total of 1377 observations were used.
[b]Log-rank test.
[c]Adjusted for all variables listed.
[d]Statistically significant.
[e]A separate multivariable model was built for each comorbid condition, with the absence of that comorbidity as the reference.

undergoing prophylactic cranial irradiation to 5.7 for patients undergoing no therapy.

In those with extensive disease, the 1-year overall survival was 22% for the patients without a comorbidity and 13% for the patients with multimorbidity (log-rank, $P < .001$; Table 6). On multivariable analysis, this effect remained (HR, 1.2 [95% CI, 1.1-1.3], model A) but disappeared after adjustment for therapy (HR, 1.1 [95% CI, 1.0-1.2], model B). This suggests that the prognostic effects of a comorbidity result from the treatment received. Nevertheless, patients with cardiac or cerebrovascular disease remained at an increased risk of death (HR, 1.2 [95% CI, 1.0-1.3] and HR, 1.3 [95% CI, 1.1-1.6], respectively). The prognosis was most strongly affected by therapy with the HR ranging from 0.4 (95% CI, 0.4-0.5) to 5.8 (95% CI, 5.1-6.5) for patients receiving prophylactic cranial irradiation and no therapy, respectively, compared with patients who received chemotherapy only.

Discussion

To the best of our knowledge, the present study is the first study on the trends in the prevalence of a comorbidity in patients with SCLC. Both comorbidity and multimorbidity were very common and had increased substantially in the previous 18 years. Although the population has aged, increased age only marginally contributed to the increased prevalence of chronic illness. The presence of multimorbidity was associated with a slightly increased hazard of death in patients with limited-stage SCLC, independent of the treatment received. More specifically, cardiac disease was associated with an increased hazard of death in those with limited-stage disease, and digestive disease reduced the hazard of death. In those with extensive-stage SCLC, multimorbidity affected the prognosis owing to the differences in therapy. The presence of cardiac disease and cerebrovascular disease increased the hazard of death in those with extensive-stage SCLC.

A recent study of patients with colorectal cancer in the same region and period as our study found similar results (ie, an increasing prevalence of comorbidities).[6] Unsurprisingly, pulmonary, vascular, and cardiac diseases (the latter only in men) were more common in those with SCLC. A Danish study of elderly patients with cancer also reported increased odds of the presence of heart disease, vascular disease, chronic obstructive pulmonary disease (COPD), ulcer disease, and renal disease in those with lung cancer compared with controls without cancer; however, no specific data on SCLC were presented.[16] The patients with lung cancer in Scotland were found to have weight loss, COPD, renal impairment, and ischemic heart disease.[17]

The trends for the increasing prevalence of concomitant diseases have not been limited to patients with cancer. The patient files of general practitioners have shown a doubling in the prevalence of chronic diseases from 1985 to 2005, and the proportion of patients with ≥ 4 chronic diseases tripled.[18]

It is probable that multiple factors have contributed to the increased prevalence of comorbidities among patients with SCLC. First, the improved care of patients with chronic diseases has affected survival, increasing the risk of developing SCLC. Second, registration effects have likely influenced our findings, because improved awareness of the importance of comorbidities among physicians might have led to better registration in the medical records and the cancer registry. Third, the improved detection of concomitant diseases during extensive screening, especially in the elderly, might have contributed to this effect. It is unlikely, however, that these registration effects could completely explain the disproportionate increases in some specific illnesses, such as hypertension (prevalence rate ratio, 2.3 for the first vs. last period), although the prevalence of pulmonary diseases only increased modestly. Fourth, lifestyle-related diseases (eg, cardiovascular disease, hypertension, and diabetes) largely accounted for the increasing prevalence of comorbidities. A less healthy lifestyle might explain the greater prevalence of comorbidities in patients with a low socioeconomic status.[19] This has also been reported for other malignancies.[5,7,17,20]

Comorbidities were more prevalent in the male patients than in the female patients. This might have been related to trends in smoking behavior, because smoking not only increases the risk of lung cancer, but also increases the risk of many other diseases, such as COPD. In our study, the increase in the prevalence of comorbidities was stronger in the women than in the men, which might have been related to the increasing proportion of women who smoked until the mid-1970s, when at the same time, the rates were decreasing among the men.[21]

Previous studies on the prognostic effect of concomitant diseases in SCLC have not led to clear associations.[3-5,22,23] In our study, the effects were dependent on the tumor stage. In those with limited-stage SCLC, we observed a slight effect of multimorbidity that was independent of the therapy selection (ie, the addition of therapy to the multivariable model increased the HR from 1.13 [95% CI, 0.97-1.32] to 1.17 [95% CI, 1.00-1.36]). However, the effects of multimorbidity in those with extensive-stage disease resulted from the treatment received. Others have reported that the comorbidity score did predict survival from SCLC, but all stages were combined.[3] However, English data have suggested that the hazards of death for patients with NSCLC and SCLC were generally not sensitive to an adjustment for comorbidities.[5,22] A small (n = 174) Canadian study did not find that the presence of a comorbidity was associated with survival in those with limited-stage SCLC from 1991 to 1999.[23] An older study of patients with SCLC in the same study region as ours found that the presence of a comorbidity had a negligible role in the survival of patients diagnosed from 1995 to 2002.[4] This was more or less in line with our findings in the final model, although the effects in those with limited-stage SCLC remained slightly increased (borderline significance). This might have been related to the larger numbers of patients, which enabled small differences to be detected in our study. Also, concomitant diseases might have played a different role after 2002, because significant associations in patients with limited-stage SCLC in the latter periods (2007 to 2012) were also observed (data not shown).

As expected, some specific comorbid conditions increased the hazard of death (eg, cardiac disease in both limited and extensive disease). Remarkable protective effects were observed, however, for digestive disease in those with limited-stage disease. These findings might be explained by some confounding factors that we did not consider, such as performance status.

Performance status was a prognostic factor considered in other studies but was not available for our study. By adjusting for the presence of comorbidities, we aimed to adjust, at least in part, for

Table 6 Crude and Multivariable Survival of Patients With Small-Cell Lung Cancer, Extensive Stage, Southern Netherlands, 1995-2012

	Crude Survival		Multivariable Survival[a]			
			Model A		Model B	
Variable	1 year (%)	*P* Value[b]	HR[c]	95% CI	HR[c]	95% CI
Sex		<.001				
Male	15		1.0		1.0	
Female	22		0.9[d]	0.8-0.9	0.8[d]	0.8-0.9
Age (years)		<.001				
<60	25		1.0		1.0	
60-69	20		1.1	1.0-1.2	1.0	0.9-1.1
70-79	11		1.4[d]	1.2-1.6	1.1	1.0-1.2
≥80	5		2.3[d]	1.9-2.8	1.1	0.9-1.4
Socioeconomic status		<.01				
Low	16		1.1	1.0-1.2	1.0	0.9-1.2
Intermediate	19		1.0	0.9-1.1	1.1	1.0-1.2
High	19		1.0		1.0	
Institutionalized	9		1.2	0.9-1.5	1.1	0.9-1.5
Unknown	9		1.4[d]	1.0-1.9	1.5[d]	1.1-2.0
Diagnostic period		<.001				
1995-1998	14		1.0		1.0	
1999-2002	10		1.0	0.9-1.2	1.1	0.9-1.2
2003-2006	16		0.9	0.8-1.0	1.0	0.9-1.1
2007-2010	22		0.8[d]	0.7-0.9	0.9	0.8-1.1
2011-2012	24		0.7[d]	0.6-0.8	0.9	0.7-1.0
Therapy						
CT only	17				1.0	
None	1				5.8[d]	5.1-6.5
Other	29				1.1	1.0-1.3
Prophylactic cranial RT	50				0.4[d]	0.4-0.5
RT plus CT	41				0.5[d]	0.4-0.6
Comorbidities		<.001				
None	22		1.0		1.0	
1	19		1.1	1.0-1.2	1.0	0.9-1.1
≥2	13		1.2[d]	1.1-1.3	1.1	1.0-1.2
Unknown	16		1.2	1.0-1.4	0.9	0.8-1.1
Comorbidity type[e]						
Diabetes mellitus	15	<.05	1.1	1.0-1.2	1.1	1.0-1.3
Other malignancy	13	<.05	1.1	0.9-1.2	1.0	0.9-1.2
Pulmonary disease	14	<.05	1.1	0.9-1.2	1.0	0.9-1.1
Cardiac disease	11	<.001	1.2[d]	1.1-1.3	1.2[d]	1.0-1.3
Vascular disease	14	<.01	1.0	0.9-1.2	1.0	0.9-1.1
Hypertension	16		1.0	0.9-1.1	0.9	0.9-1.1
Cerebrovascular disease	8	<.001	1.4[d]	1.1-1.6	1.3[d]	1.1-1.6
Digestive disease	15		1.1	0.9-1.3	1.0	0.8-1.2

Abbreviations: Adj = adjuvant therapy; CI = confidence interval; CT = chemotherapy; HR = hazard ratio; RT = radiotherapy.
[a]A total of 2355 observations were used.
[b]Log-rank test.
[c]Adjusted for all variables listed.
[d]Statistically significant.
[e]A separate multivariable model was built for each comorbid condition with the absence of comorbidity as the reference.

patient fitness, because the severity of a number of comorbidities predicted the performance status in patients with lung cancer.[24] The absence of information on performance status, combined with an absence of information on smoking status, could also have contributed to our findings that digestive disease was associated with a reduced risk of death in patients with limited-stage SCLC.

The presence of a comorbidity might negatively affect the prognosis of patients with cancer because it delayed the detection of the cancer. In our study population, stage did not differ between patients with and without a comorbidity (in both groups, 34% had limited disease), just as has been reported previously.[17] However, patients with lung cancer living in southeast England and the United States with comorbidities were more likely to be diagnosed with early-stage disease.[5] In Denmark, an increase in comorbidities was also reported to have a slight, but not significant, effect on the staging process.[25,26] We stratified the analyses by stage; however, subgroups within a stage might exist. In addition, concomitant diseases might affect the treatment of SCLC,[3,5] and thereby the prognosis, just as we observed for patients with extensive disease. However, a slight prognostic effect of multimorbidity was observed in those with limited-stage SCLC after adjustment for treatment, suggesting that multimorbidity in itself might affect the prognosis. Nevertheless, the prognostic effects of therapy were much stronger than the effects of the presence of comorbidities. We had no information on the dosage or whether a patient had completed the treatment. Both these factors likely would be negatively affected by the presence of comorbidity.

One advantage of our study was the long-standing, prospective, routine registration of the presence of comorbidities at the diagnosis. The extraction methods have not changed, and clearly defined extraction methods were maintained throughout the study period. Only well-educated and trained registry personnel performed the registration, and our results were routinely checked internally. For lung cancer in general, however, the overall rate of under registration was 8% in 1995, mainly for cardiovascular disease (27%).[27] This also might have influenced our findings, although the methods of registration had improved in 1996.

Another strength of our study was the population-based approach, with a large sample size of consecutive, unselected patients, regardless of treatment. This is the first study to investigate the trends in the prevalence of comorbidities in an unselected group of patients with SCLC.

Our study was limited by an absence of data on disease-specific survival. We expect that overall survival would correlate with SCLC survival rather well, given the high lethality of the disease. Furthermore, we were only able to include patients with a histologic or cytologic diagnosis of SCLC, not those with suspected eligibility. This will have affected our findings, because a bias might have resulted from the use of different diagnostic procedures. Also, the data required for histologic or cytologic confirmation might have changed during the study period, with a range of 5% to 11% of all lung cancer cases not histologically confirmed during the study period (no trend).

Although a considerable and increasing proportion of patients with SCLC will have comorbidity, these patients have often been excluded from trials. We would, therefore, advise the inclusion of these patients in trials, because it would provide a basis for clinical practice guidelines regarding the treatment of patients with comorbidities.

In addition, healthcare providers should remain aware of the common comorbidities when coordinating a patient's care, because the presence of comorbidities requires increased coordination among multiple disciplines. Furthermore, healthcare providers should be aware of the potential interactions (both disease and treatment related) that could lead to greater susceptibility to polypharmacy and adverse drug effects. Careful monitoring of the possible side effects and increased awareness to identify possible adverse drug effects are needed.

Conclusion

The presence of comorbidity among patients with SCLC is very common and has been increasing. Multimorbidity affected survival in those with extensive-stage SCLC owing to differences in treatment. A slight prognostic effect was observed, independent of treatment, in the patients with limited-stage disease. More specifically, digestive (limited-stage), cardiac (limited- and extensive-stage), and cerebrovascular (extensive-stage) disease affected the prognosis. With the burden of comorbidities in patients with SCLC increasing, more attention to individualized treatment approaches is needed.

Clinical Practice Points

- Data on the trends of comorbidities in patients with SCLC are scarce. Previously, the presence of comorbidity was shown to affect treatment. Whether the presence of comorbidity also affects the prognosis of patients with SCLC is not yet clear, because both negative prognostic effects and the absence of an effect have been reported.
- The prevalence of comorbidities has increased, in particular, hypertension, diabetes mellitus, and cardiac and pulmonary diseases have become more common. Multimorbidity (ie, ≥ 2 comorbid conditions) was associated with a slightly increased hazard of death, independent of treatment in those with limited-stage SCLC. However, the prognostic effects of multimorbidity resulted from the treatment received in those with extensive-stage SCLC. The prognostic effect of specific comorbidities varied, with digestive disease reducing the hazard and cardiac disease increasing the hazard in those with limited-stage disease, and cardiac and cerebrovascular disease increasing the hazard in those with extensive-stage disease.
- These data are of relevance with regard to the treatment decisions and patient communication in daily clinical practice. As the burden of comorbidities in patients with SCLC increases, more attention to individualized treatment approaches is needed.

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Disclosure

The authors have stated that they have no conflicts of interest.

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