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Charlson comorbidity index as a predictor of long-term outcome after surgery for nonsmall cell lung cancer☆

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Abstract

Objective: To evaluate the impact of the Charlson comorbidity index on long-term survival in nonsmall cell lung cancer surgery and determine whether this index is a better predictor of long-term survival than individual comorbid conditions. **Methods:** From January 1989 to December 2001, 433 (340 men, 93 women) consecutive curative resections for nonsmall cell lung cancer were performed. Each patient was preoperatively assessed according to the Charlson comorbidity index. Survival curves were estimated by the Kaplan—Meier method. Risk factors for overall and disease free survival were determined by univariate and multivariate Cox regression analysis. **Results:** The patients ranged in age from 37 to 82 years, with a mean age of 65 years. Hospital mortality was 3.7%. Five-year overall and disease free survival was 45 and 43%, respectively. Among patients with Charlson comorbidity grade 0, 5-year overall survival was 52%, among patients with Charlson comorbidity grade 1—2 it was 48%, and among patients with Charlson comorbidity grade ≥3 it was 28%. Univariate analysis showed that male gender, age, congestive heart failure, chronic pulmonary disease, Charlson comorbidity index, clinical stage, pathological stage, and type of resection were significantly associated with an impaired survival. Multivariate analysis showed that age (relative risk, 1.02; 95% confidence interval, 1.01—1.03), Charlson comorbidity grade 1—2 (relative risk, 1.4; 95% confidence interval, 1.0—1.8), Charlson comorbidity grade ≥3 (relative risk, 2.2; 95% confidence interval, 1.5—3.1), bilobectomy (relative risk, 1.7; 95% confidence interval, 1.2—2.5), pneumonectomy (relative risk, 1.5; 95% confidence interval, 1.1—2.0), pathological stage IB (relative risk, 1.5; 95% confidence interval, 1.1—2.2), IIB (relative risk, 1.9; 95% confidence interval, 1.2—3.0), IIIA (relative risk, 1.9; 95% confidence interval, 1.1—3.1), IIIB (relative risk, 2.8; 95% confidence interval, 1.2—6.8), and IV (relative risk, 12.4; 95% confidence interval, 3.2—48.2), were associated with an impaired survival. **Conclusions:** The Charlson comorbidity index is a better predictor of survival than individual comorbid conditions in nonsmall cell lung cancer surgery. We recommend the use of a validated comorbidity index in the selection of patients for NSCLC surgery.

Keywords: Charlson comorbidity index; Comorbidity; Lung cancer; Surgery; Survival

1. Introduction

Although pulmonary resection is recognized as the treatment of choice for early-stage nonsmall cell lung cancer (NSCLC), actuarial 5-year survival following curative resection is disappointing, ranging from 67 to 38% in pathological stages IA—IIB [1]. Survival is not only dependent on pathological stage but also on other factors, such as comorbidity. The presence of comorbidity has been evaluated repeatedly as an important prognostic factor for survival in patients with NSCLC [2—4]. As the mean age in patients with NSCLC increases due to the increased life expectancy, the proportion of patients with serious comorbidity who are considered for surgical resection also increases [5,6]. For major postoperative complications the Charlson comorbidity index (CCI) proved to be a prognostic marker as was previously validated by us in patients operated on for primary NSCLC [7]. However, this comorbidity index has not been validated yet for prognostic impact on long-term survival in NSCLC surgery.

Therefore, the objective of this retrospective study was to evaluate the impact of the CCI on long-term survival in NSCLC surgery and determine whether this index is a better predictor of long-term survival than individual comorbid conditions.

2. Materials and methods

The medical records of 433 consecutive patients who underwent curative resection for primary NSCLC at the Department of Cardio-Thoracic Surgery of the Erasmus MC Rotterdam between January 1, 1989, and December 31, 2001 were reviewed. Patients were followed with regular visits to

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the outpatient clinic. Civil administrations were consulted to assess late mortality. Follow-up was completed in all patients through August 2004. Median follow-up time was 4.3 years (range, 0.0–14.9 years). Overall survival time was defined as the difference between the date of surgery and the date of last follow-up. Disease free survival time was defined as the difference between the date of surgery and the date of local or distant recurrence of disease or the date of last follow-up in case of no recurrence. Hospital mortality was defined as death occurring within 30 days of surgery or any death later during the same postoperative hospital stay.

In all patients preoperative diagnostic workup included a complete medical history, physical examination, plain chest radiography, electrocardiography, routine laboratory tests, lung function tests and computed tomography of the chest and upper abdomen. Additional staging procedures, i.e. mediastinoscopy, liver, bone and brain scans were selectively performed to aid in treatment planning according to best clinical practice at the time of presentation. Each patient was assessed preoperatively according to the CCI, and was categorized in one of the four comorbidity grades: 0, 1–2, 3–4 and 5 or more [7,8].

Histological typing occurred according to The World Health Organization Histological Typing of Lung Tumours [9]. Clinical and pathologic staging of the patients occurred according to the international TNM classification for lung cancer [1].

The following risk factors for overall and disease free survival were evaluated: sex, age, smoking, type of resection, histological cell type, forced expiratory volume in 1 s (FEV_1; unknown in 21 patients), clinical stage, pathological stage, and the CCI as well as the most common comorbidities of the CCI.

2.1. Statistical analysis

Discrete variables are displayed as proportions, continuous variables as means ± standard deviations unless specified otherwise. The χ^2 or Fisher exact test was used to analyze the categorical data. Continuous variables were analyzed using the unpaired Student *t*-test. Survival curves were estimated by the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard analysis within different time intervals determined risk factors for survival. The Cox proportional multivariate analyses were performed with a stepwise forward regression model in which each variable with a *p*-value of less than 0.20 in the univariate analysis was entered in the model. Relative risks are reported with 95% confidence intervals. All data analysis was performed with SPSS for Windows (release 12.0; SPSS Inc., Chicago, IL).

3. Results

Of the 433 patients included in this analysis, 340 (79%) were men and 93 (21%) women. The mean age at time of diagnosis was 65 ± 9 years (range, 37–82 years). The patient's preoperative characteristics are outlined in Table 1. The CCI and the comorbid conditions are presented in Table 2. The types of procedures performed consisted of a wedge resection in 14 (3%) patients, a lobectomy in 244 (56%) patients, a bilobectomy in 45 (10%) patients, and a pneumonectomy in 130 (30%) patients. Tumours were classified histologically as squamous cell carcinoma (215; 50%), adenocarcinoma (143; 33%), large cell carcinoma (55; 13%), and bronchoalveolar cell carcinoma (20; 5%). The patient's operative demographics are listed in Table 3.

Table 1
Patient characteristics

Characteristic	No. of patients	%
Sex		
Male	340	79
Female	93	21
Age (mean ± SD in years)	65 ± 9	
Median follow-up in years (range)	4.3 (0.0–14.9)	
Smoking habits		
Nonsmoker	57	13
Current or former smoker	376	87
FEV_1%[a]		
<70	115	28
≥70	297	72
Charlson comorbidity index		
0	131	30
1–2	220	51
3–4	75	17
≥5	7	2
Clinical stage		
IA	202	47
IB	185	43
IIA	5	1
IIB	22	5
IIIA	13	3
IIIB	3	1
IV	3	1

SD, standard deviation.
[a] FEV_1%, forced expiratory volume in 1 s expressed as a percent of predicted; unknown in 21 patients.

Table 2
Charlson comorbidity index and prevalence of comorbid conditions

Score	Condition	No. of patients	%
1	Coronary artery disease[a]	90	21
	Congestive heart failure	30	7
	Chronic pulmonary disease	126	29
	Peptic ulcer disease	46	11
	Peripheral vascular disease	86	20
	Mild liver disease	1	0
	Cerebrovascular disease	34	8
	Connective tissue disease	7	2
	Diabetes	24	6
	Dementia	2	1
2	Hemiplegia	2	1
	Moderate to severe renal disease	2	1
	Diabetes with end organ damage	2	1
	Any prior tumor (within 5 years of diagnosis)[b]	60	14
	Leukemia	5	1
	Lymphoma	4	1
3	Moderate to severe liver disease	3	1
6	Metastatic solid tumor	0	0
	AIDS (not only HIV positive)	0	0

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.
[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris.
[b] Except basal cell skin carcinoma.

Table 3
Operative characteristics

Characteristic	No. of patients	%
Type of resection		
Wedge resection	14	3
Lobectomy	244	56
Bilobectomy	45	10
Pneumonectomy	130	30
Histology		
Squamous cell carcinoma	215	50
Adenocarcinoma	143	33
Large cell carcinoma	55	13
Bronchoalveolar cell carcinoma	20	5
Pathological stage		
0	1	0
IA	153	35
IB	154	36
IIA	21	5
IIB	52	12
IIIA	36	8
IIIB	7	2
IV	9	2

Surgical-pathologic upstaging was observed in 31% (133/433) of the patients.

Hospital mortality was 3.7% (16/433). Operations in these patients were wedge resection (1), lobectomy (4), bilobectomy (3), and pneumonectomy (8). Hospital mortality rate was significantly ($p = 0.03$) higher after pneumonectomy compared with lesser resections. One, 2 and 5-year overall survival was 81% (95% confidence interval 77–85), 66% (95% confidence interval 62–71), and 45% (95% confidence interval 40–50), respectively. One, 2, and 5-year disease free survival was 74% (95% confidence interval 70–78), 61% (95% confidence interval 56–65), and 43% (95% confidence interval 38–48), respectively. Among patients with Charlson comorbidity grade 0, 5-year overall survival was 52% (95% confidence interval 43–61), among patients with Charlson comorbidity grade 1–2 it was 48% (95% confidence interval 39–57), and among patients with Charlson comorbidity grade ≥3 it was 28% (95% confidence interval 18–38) (Fig. 1). When evaluating risk factors for overall survival with the Cox proportional hazards analysis, in univariate analysis male gender, age, congestive heart failure, chronic pulmonary disease, CCI, clinical stage, pathological stage, and type of resection were significantly associated with an impaired survival (Table 4). In multivariate analysis, age (relative risk, 1.02; 95% confidence interval, 1.01–1.03), Charlson comorbidity grade 1–2 (relative risk, 1.4; 95% confidence interval, 1.0–1.8), Charlson comorbidity grade ≥3 (relative risk, 2.2; 95% confidence interval, 1.5–3.1), bilobectomy (relative risk, 1.7; 95% confidence interval, 1.2–2.5), pneumonectomy (relative risk, 1.5; 95% confidence interval, 1.1–2.0), pathological stage IB (relative risk, 1.5; 95% confidence interval, 1.1–2.2), IIB (relative risk, 1.9; 95% confidence interval, 1.2–3.0), IIIA (relative risk, 1.9; 95% confidence interval, 1.1–3.1), IIIB (relative risk, 2.8; 95% confidence interval, 1.2–6.8), and IV (relative risk, 12.4; 95% confidence interval, 3.2–48.2), were associated with an impaired overall survival (Table 4). For disease free survival the same risk factors were identified in the multivariate analysis.

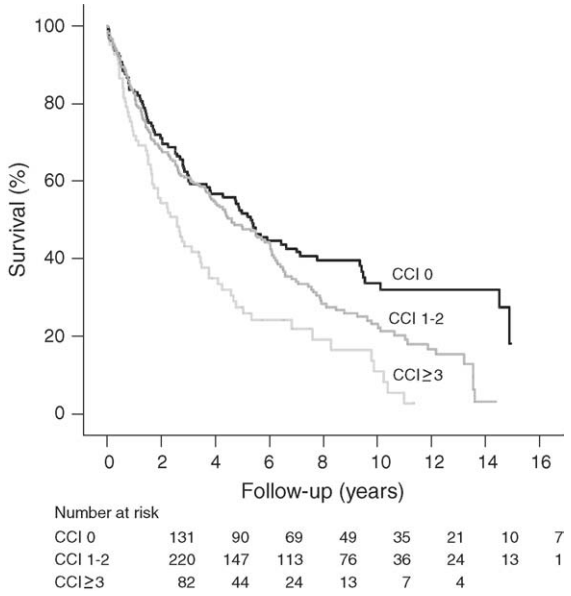

Fig. 1. Overall survival curves after curative resection for nonsmall cell lung cancer according to the Charlson comorbidity index (CCI).

4. Discussion

Not unexpectedly, pathological stage proved to be an important determinant of long-term survival in this study. Surgical-pathological upstaging was seen in 31% of the patients. Obviously, clinical staging with current imaging techniques has its shortcomings indicating the need for further improvement of preoperative staging techniques. Besides tumor stage, in patients with NSCLC comorbid conditions also play a significant role in clinical practice treatment decisions and patients whose outcomes are judged unfavourable because of serious comorbidity are usually selected for non-surgical management. Many reports in the literature have shown the prognostic impact of comorbidity on survival in NSCLC surgery [2,4,10,11]. Summarizing a multidimensional phenomenon such as comorbidity is not an easy matter, and currently no standard method exists for assessing comorbidities collectively in NSCLC surgery patients. In this study the CCI was used to assess comorbidity. This comorbidity index has been used in several clinical studies [12–14] and has previously been validated by us for prediction of major postoperative complications after NSCLC surgery [7]. In this analysis comorbidity severity had a significant negative impact on long-term survival when comorbidity was assessed according to the CCI. After controlling for age, gender, type of resection, clinical stage, pathological stage, and individual comorbid conditions in a multivariate analysis, the relative risk of impaired survival as a function of the CCI was 1.4 times higher among patients with Charlson comorbidity grade 1–2, and 2.2 times higher among patients with Charlson comorbidity grade ≥3 compared with patients with no comorbidity. This indicates that the CCI is a better predictor of survival than individual comorbid conditions and validates the ability of the CCI to stratify comorbidity severity in NSCLC surgery patients.

The management of patients with NSCLC remains a significant challenge. Comorbidity is common in NSCLC

Table 4
Univariate and multivariate Cox proportional hazard analysis of overall survival

Variable	No. of Patients	Univariate		Multivariate	
		RR	95% CI	RR	95% CI
Male sex	340	1.6	1.2–2.2		
Age	433	1.02	1.01–1.03	1.02	1.01–1.03
Current or former smoker	376	0.9	0.6–1.2		
FEV_1% ≤70	115	1.2	0.9–1.6		
Wedge resection	14	2.2	1.3–3.9		
Bilobectomy	45	1.7	1.2–2.4	1.7	1.2–2.5
Pneumonectomy	130	1.5	1.2–1.9	1.5	
Squamous cell carcinoma	215	1.1	0.9–1.4		
Coronary artery disease[a]	90	1.2	0.9–1.6		
Congestive heart failure	30	1.8	1.2–2.7		
Chronic pulmonary disease	126	1.5	1.1–1.9		
Peptic ulcer disease	46	1.1	0.8–1.6		
Peripheral vascular disease	86	1.2	0.9 – 1.5		
Cerebrovascular disease	34	1.2	0.8–1.7		
Diabetes	24	0.9	0.6–1.5		
Any prior tumor (within 5 years of diagnosis)[b]	60	1.3	0.9–1.8		
Charlson comorbidity index					
1–2	220	1.3	1.0–1.8	1.37	1.02–1.84
≥3	82	2.1	1.5–2.9	2.2	1.5–3.1
Clinical stage					
IB	185	1.3	1.0–1.7		
IIA	5	3.0	1.2–7.5		
IIB	22	2.3	1.4–3.8		
IIIA	13	2.1	1.1–3.8		
IIIB	3	1.5	0.4–6.1		
IV	3	15.7	4.8–50.9		
Pathological stage					
IB	154	1.5	1.1–1.9	1.5	1.1–2.2
IIA	21	1.0	0.5–1.7	0.7	0.4–1.4
IIB	52	1.7	1.2–2.4	1.9	1.2–3.0
IIIA	36	2.1	1.3–3.2	1.9	1.1–3.1
IIIB	7	2.6	1.1–5.8	2.8	1.2–6.8
IV	9	10.2	5.0–20.7	12.4	3.2–48.2

RR, relative risk; CI, confidence interval; FEV_1%, forced expiratory volume in 1 s expressed as a percent of predicted; unknown in 21 patients.
[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris.
[b] Except basal cell skin carcinoma.

patients and has a major impact on their survival, independent of other factors. Our study shows the importance of the CCI as an independent prognostic factor for impaired survival. This comorbidity index is a better predictor of long-term survival than individual comorbid conditions. We recommend the use of a validated comorbidity index in the selection of patients for NSCLC surgery.

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