ORIGINAL ARTICLE

The Influence of Comorbidity and the Simplified Comorbidity Score on Overall Survival in Non-Small Cell Lung Cancer—A Prospective Cohort Study

Marliese Alexander, B.Pharm (Hons), MPH,[a,b,*] Sue M. Evans, BN, MCE, PhD,[a] Robert G. Stirling, BSc (Hons), MBBCh, MRCPI, FRACP,[a,d] Rory Wolfe, BSc, PhD,[a] Ann Officer, RN B.Ed.,[e,f] Michael MacManus, MD,[f] Benjamin Solomon, M.B.B.S., PhD, FRACP,[e,g] Kate Burbury, M.B.B.S. (Hons), FRACP, FRCPA, PhD,[c] David Ball, M.B.B.S., MD[f,g]

[a]*Department of Epidemiology and Preventive Medicine, Monash University Melbourne, Australia*
[b]*Division of Cancer Medicine, Peter MacCallum Cancer Centre, Melbourne, Australia*
[c]*Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia*
[d]*Department of Allergy Immunology and Respiratory Medicine, Alfred Health, Melbourne, Australia*
[e]*Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*
[f]*Department of Radiation Oncology (Lung Service), Peter MacCallum Cancer Centre, Melbourne, Australia*
[g]*Sir Peter MacCallum Department of Oncology, The University of Melbourne, Parkville, Australia*

Received 11 November 2015; revised 21 January 2016; accepted 26 January 2016
Available online - 3 February 2016

ABSTRACT

Introduction: We addressed the uncertainty of comorbidity as a prognosticator by evaluating comorbidity and the Simplified Comorbidity Score (SCS) as predictors of overall survival in non–small cell lung cancer (NSCLC).

Methods: A prospective study included patients in whom NSCLC was diagnosed at an Australian cancer hospital between 2012 and 2014. Patients were assessed for SCS at recruitment and followed up every 3 months until death.

Results: The cohort included 633 patients; their median age was 67 years (range 28–93), 63% were male, and 86% were ever-smokers. The median SCS at enrolment was 8 (range 0–19); 20% had an SCS higher than 9, and 11% had an SCS of 0. An SCS higher than 9 was associated with male sex, age older than 75 years, an Eastern Cooperative Oncology Group performance status of 2 or higher, and fewer cancer treatments. The 1-year overall survival rate was 62% (95% confidence interval: 58–66). In multivariate analysis, the strongest associations with mortality were metastatic disease (hazard ratio [HR] = 2.8, $p < 0.01$), Eastern Cooperative Oncology Group performance status of 2 or higher (HR = 2.0, $p < 0.01$), male sex (HR = 1.6, $p < 0.01$), more than 10% weight loss at diagnosis (HR = 1.5, $p < 0.01$), and age older than 75 years (HR = 1.5, $p = 0.01$). An SCS higher than 9 was not associated with overall survival (HR = 1.0, $p = 0.8$), and the effect of continuous SCS (HR = 1.1, $p < 0.01$) was explained by smoking status.

Conclusions: In this cohort of patients with NSCLC the SCS was not a clinically significant predictor of overall survival over and above basic patient and disease factors.

Keywords: Comorbidity; Simplified comorbidity score; Lung cancer; Survival; Risk score

Background

Lung cancer, a smoking related cancer with a sharply rising incidence in the over-60 population, is associated with a high level of both smoking-related and non–smoking-related comorbidity.[1] The importance of comorbid conditions to the prognosis of patients with lung cancer remains contentious, but they likely negatively

*Corresponding author.

Drs. Burbury and Ball contributed equally to this article.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Marliese Alexander, B.Pharm (Hons), MPH, Peter MacCallum Cancer Centre, Locked Bag 1 A'Beckett Street, Victoria 8006 Australia. E-mail: Marliese.Alexander@petermac.org

ISSN: 1556-0864
http://dx.doi.org/10.1016/j.jtho.2016.01.016

affect survival directly or through effects on performance status and deliverability and tolerability of treatment.

The prognostic value of comorbidity in lung cancer survival has been widely investigated.[2–24] The two most utilized comorbidity risk scores are the Charlson Comorbidity Index (CCI) and the more recently developed Colinet Simplified Comorbidity Score (SCS).[3,25] The CCI was originally developed in a noncancer population but has since been validated in many cancer populations, including lung cancer populations. The SCS was developed and validated in a cohort of patients with non–small cell lung cancer (NSCLC) with its intended use specifically in this population. Derivation within a lung cancer population and inclusion of fewer parameters than in the CCI make the SCS an appealing tool for prognostication of lung cancer.

The predictive value of the SCS remains unclear, however, with few published studies and divergent findings. Since publication of the SCS in 2005,[3] four studies have evaluated its prognostic value: one in NSCLC,[4] one in SCLC,[6] and two in mixed NSCLC/SCLC cohorts.[2,5] One study each in NSCLC and in SCLC demonstrated an increased risk of mortality with elevated SCS (score >9 versus ≤ 9).[4,6] However, the remaining two studies found no association between the SCS and mortality.[2,5] A recent review of the effect of comorbidity on cancer survival reported minimal impact of comorbid conditions on the 5-year survival of patients with lung cancer relative to patients with other cancer diagnoses.[26] A plausible explanation posed by the authors is that that the poor survival outcome for lung patients with cancer generally means that any effect of comorbid disease on a relative scale is small.

The primary objective of this study was to evaluate the capability of the SCS to predict overall survival in a prospective cohort study of patients with NSCLC who were staged with the seventh edition of the tumor, node, and metastasis system (Union for International Cancer Control).[27] Secondary objectives included evaluation of overall comorbidity burden and the prognostic significance of individual comorbidities.

Methods

Population

The population for analysis was derived from the Peter MacCallum Cancer Centre Thoracic Malignancies Cohort (TMC) study, an ongoing single-center prospective observational study designed to monitor patients with lung cancer from first presentation until death. The TMC began recruiting in 2012 with approval of the institutional ethics committee. The TMC eligibility criteria included presentation to the lung cancer service of an Australian tertiary referral cancer hospital, diagnosis of lung or other respiratory/mediastinal cancer, and provision of informed consent. Further eligibility criteria for the current study included a histological diagnosis of NSCLC between January 1, 2012, and December 31, 2014, and at least one study follow-up after diagnosis. The earliest diagnosis date was restricted to January 1, 2012, to limit inclusion to only newly diagnosed cases from the TMC and thereby prevent survival bias associated with inclusion of long-term survivors enrolled in the TMC for ongoing treatment and/or surveillance.

Data

Data were collected by completion of a case report form at study entry and then periodically (every 3 months) at routine clinical appointments. The case report forms were completed by a dedicated project officer and verified by the treating clinician. Data included patient demographics, comorbid disease, cancer diagnosis, staging, and treatment. Staging was reported according to the seventh edition of the Union for International Cancer Control staging criteria,[27] which are based on the recommendations of the International Association for the Study of Lung Cancer staging project.[28] Comorbidities were documented at first consultation and defined according to the SCS, which includes the following health events (weighting in parentheses): past or current tobacco consumption (7), diabetes mellitus (5), renal insufficiency (4), respiratory comorbidity (1), cardiovascular comorbidity (1), neoplastic comorbidity (1), and alcoholism (1).[3] Performance status was reported according to the Eastern European Cooperative Group performance status (ECOG PS) criteria.[29] Loss of weight (LOW) refers to weight loss within 3 months of diagnosis and was analyzed categorically as 0% to 10%, 11% to 15%, or more than 15%. Smoking history was defined as current, past, or never, and when relevant, pack-years smoked and years since cessation of smoking were recorded.

Statistical Analyses

Data were summarized using descriptive statistics—for continuous variables, median, minimum, and maximum, and for categorical variables, counts and percentages. All statistical tests to compare comorbidity burden with other characteristics were performed using a two-sided significance level of 5% and corresponding 95% confidence intervals (CIs) were calculated. The association of SCS with patient, disease, and treatment factors was assessed using the chi-square statistic. SCS was assessed as a continuous variable, at a predefined threshold of higher than 9 versus 9 or lower,[3] and at various other thresholds. Survival probability was estimated using the Kaplan-Meier method and was calculated from date of tissue diagnosis until date of death, with living patients considered censored at date of last

study follow-up. Median follow-up was calculated for living patients. Patient status (dead versus alive) was established every 3 months either at attendance of a review or during a phone call to the patient or general practitioner. Final extraction of data from the TMC occurred on December 31, 2015. The association of covariates with overall survival was assessed by undertaking univariate and multivariate Cox proportional hazards regression. Interaction terms were utilized to assess for potential confounding effects of covariates, and when they were present, stratified analyses were undertaken. Additional analyses were conducted for the subgroup of patients diagnosed before December 31, 2013, to investigate the impact of longer follow-up duration. All statistical analyses were performed using Stata 12.1 software.[30]

Results

During the study period 826 patients were enrolled in the TMC and screened for this substudy. The final cohort for analysis included 633 patients, with patients excluded for the following reasons: diagnosis other than NSCLC (SCLC [n = 59], thymoma [n = 33], mesothelioma [n = 24], neuroendocrine malignancy [n = 22], or other lung malignancy [n = 8]), no tissue diagnosis (n = 10), missing date of tissue diagnosis (n = 3), no follow-up after diagnosis (n = 12), and missing or incomplete comorbidity data (n = 22). Baseline demographics, disease characteristics, and comorbidities are described in Table 1. Almost all patients received anticancer treatment (94%), curative chemoradiotherapy (22%), curative radiotherapy (10%), curative surgery (19%), chemotherapy (35%), or biologic therapy (17%).

Comorbidity

Few patients had no SCS comorbidities (11%) compared with one comorbidity (26%), two comorbidities (30%), and three or more comorbidities (33%). The median SCS was 8, with 65% of patients having an SCS between 7 and 9 and 20% having an SCS higher than 9. Ever-smokers (86% of patients) had a higher total comorbidity burden; 72% of ever-smokers compared with 27% of never-smokers had at least one comorbidity other than smoking ($p < 0.01$). Of the ever-smokers, 24% had an SCS higher than 9, whereas all the never-smokers had an SCS of 9 or lower. Ever-smokers had higher comorbidity domain scores compared with never-smokers: for alcoholism, 8% versus 1% ($p = 0.02$); for diabetes, 15% versus 7% ($p = 0.09$); for renal insufficiently, 5% versus 3% ($p = 0.40$); for cardiovascular

Table 1. Patient Characteristics

	NSCLC (n = 633)	
Characteristics	n	%
Patient factors		
Male sex	399	63.0
Median age (range), y	67 (28-93)	
White	528	83.4
Asian	77	12.2
Other race	28	4.4
Comorbidity		
MedianSCS (IQR)	8 (7-9)	
SCS >9	128	20.2
Alcoholism	43	6.8
Diabetes mellitus	87	13.7
Renal insufficiency	32	5.1
Cardiovascular comorbidity	170	26.9
Respiratory comorbidity	215	33.9
Neoplastic comorbidity	169	26.7
Tobacco		
Ever-smoker	541	85.5
Current	118	18.6
Past	423	66.8
Never	92	14.5
Median pack-years (IQR)	41 (25-57)	
LOW 0%-10%	513	81.0
11%-15%	91	14.4
>15%	29	4.6
ECOG PS 0	116	18.3
1	389	61.5
2	92	14.5
3	36	5.7
Disease factors		
Stage group *(IASLC, seventh edition)*		
IA	51	8.1
IB	51	8.1
IIA	24	3.8
IIB	35	5.5
IIIA	105	16.6
IIIB	62	9.8
IV	305	48.1
NSCLC histological diagnosis		
Adenocarcinoma	387	61.1
Squamous cell carcinoma	167	26.4
NOS NSCLC	59	9.3
Other NSCLC[a]	20	3.2
Actionable mutation (any)	152	24.0
EGFR	66	10.4
ALK	29	4.6
BRAF	58	9.2

[a]Other NSCLC includes 10 large cell cancers, 7 adenosquamous carcinomas, and 3 mixed NSCLCs/SCLCs.

ALK, anaplastic lymphoma receptor tyrosine kinase gene; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase gene; ECOG PS, Eastern European Cooperative Group performance status; *EGFR*, epidermal growth factor receptor gene; IASLC, International Association for the Study of Lung Cancer; IQR, interquartile range; LOW, loss of weight; NSCLC, non-small cell lung cancer; NOS, not otherwise specified; SCS, simplified comorbidity score.

Table 2. Associations of Patient, Disease, and Treatment Factors with SCS Greater Than 9

	SCS ≤ 9 (n = 505)		SCS > 9 (n = 128)		
Variable	n	%	n	%	*p* Value[a]
Patient factors					
Male	298	59.0	101	78.9	<0.01
Age >75 y	111	22.0	54	42.2	<0.01
ECOG PS ≥2	90	17.8	38	29.7	<0.01
LOW >10%	88	17.4	32	25.0	0.05
Disease factors					
Stage III-IV disease	385	76.2	87	68.0	0.06
Stage IV disease	252	49.9	53	41.4	0.09
Treatment factors					
Curative surgery	102	20.2	19	14.8	0.17
Curative chemoradiotherapy	114	22.6	26	20.3	0.58
Curative radiotherapy	38	7.5	25	19.5	<0.01
Chemotherapy[b]	192	38.0	28	21.9	<0.01
Biologic therapy	99	19.6	7	5.5	<0.01

[a]*p* Value for the comparison of % SCS >9 with % SCS ≤9.
[b]Chemotherapy other than combined modality chemoradiotherapy.
ECOG PS, Eastern European Cooperative Group Performance Status; LOW, loss of weight; SCS, Simplified Comorbidity Score.

comorbidity, 30% versus 9% ($p < 0.01$); for respiratory comorbidity, 39% versus 8% ($p < 0.01$); and for neoplastic comorbidity, 30% versus 10% ($p < 0.01$). Patient- and treatment-related factors associated with SCS are described in Table 2.

Survival

Median follow-up for the cohort was 21 months (range 0.3–48), during which time 360 of 633 patients (57%) died. Median overall survival was 17 months (range 0.3–48). The 1- and 2-year overall survival rates were 62% (95% CI: 58–66) and 41% (95% CI: 37–45). Subanalysis of survival outcomes in patients diagnosed before December 31, 2013, extended the median follow-up duration to 29 months (range 0.3–48), during which time 254 of 429 patients (59%) died.

Median overall survival for patients with stage I disease was not reached (range 3.6–44), for patients with stage II disease it was 34 months (range 3.3–33), for patients with stage IIIA disease it was 23 months (range 0.9–32), for those in stage IIIB it was 13 months (0.9-26), and for those in stage IV it was 10 months (range 0.3–37).

Comorbidity and Survival

In univariate analysis (Table 3), smoking significantly increased mortality risk; risk was similar for all past smokers versus current smokers (hazard ratio [HR] = 1.1, 95% CI: 0.9–1.5, $p = 0.6$) and for long-term past smokers (cessation more than 10 years before diagnosis) versus current smokers (HR = 1.0, 95% CI: 0.7–1.3, $p = 0.4$). In particular, years since cessation ($p = 0.6$) and pack-year history ($p = 0.2$) did not predict survival among ever-smokers. In other univariate analyses, SCS was associated with increased mortality risk only when analyzed as a continuous variable (HR per single SCS point = 1.1, 95% CI: 1.0–1.1, $p < 0.01$) but not when assessed at the predefined threshold of higher than 9 verses 9 or lower (HR = 1.0, 95% CI: 0.8–1.3, $p = 0.8$) (Fig. 1). In contrast, ECOG PS (≥2 versus <2) was associated with increased mortality risk (HR = 2.2, 95% CI: 1.7–2.8, $p < 0.01$) (Fig. 2).

In multivariate analysis (adjusted for stage, ECOG PS ≥2, LOW ≥10%, age >75, and male sex), other than smoking status, respiratory comorbidity was the only predictor of mortality within the SCS (HR = 1.7, 95% CI: 1.4–2.1, $p < 0.01$) (Table 3). An adjusted association between continuous SCS and mortality existed for the entire cohort (HR = 1.07 per single SCS point, 95% CI: 1.04–1.10, $p < 0.01$) and for the cohort of those whose disease was diagnosed in or before 2013 (HR per single SCS point = 1.08, 95% CI: 1.04–1.12, $p < 0.01$). However, this association was accounted for with the addition of smoking status (ever versus never) to the model (adjusted HR per single SCS point for the entire cohort = 1.01, 95% CI: 0.96–1.07, $p = 0.69$). Stratified analysis of the entire cohort found that continuous SCS was not associated with mortality among past smokers (HR per single SCS point = 1.00, 95% CI: 0.95–1.05, $p = 0.9$) or current smokers (HR per single SCS point = 1.01, 95% CI: 0.92–1.12, $p = 0.8$), but interestingly, it demonstrated a nonsignificant trend for increased mortality in never-smokers (HR per single SCS point = 1.20, 95% CI: 1.00–1.45, $p = 0.06$). Dichotomized SCS (>9 versus ≤9) was not associated with mortality in the entire cohort (HR = 0.9, 95% CI: 0.7–1.2, $p = 0.8$) or in the cohort diagnosed in or before 2013 (HR = 0.9, 95% CI: 0.6–1.12, $p = 0.3$). Moreover, the adjusted association between an altered SCS threshold (>7 versus ≤7) and mortality (HR = 1.6, 95% CI: 1.3–2.1, $p < 0.01$) was also accounted for by additional adjustment for smoking status. In analysis restricted to ever-smokers, an SCS higher than 7 versus 7 or lower was not associated with mortality (HR = 1.2, 95% CI: 0.9–1.6, $p = 0.1$), nor was any other SCS threshold. In never-smokers, however, an SCS higher than 1 versus 1 or lower was associated with an increased mortality risk (HR = 2.6, 95% CI: 1.0–6.3, $p = 0.04$), although other SCS thresholds did not exhibit such an association.

Key findings from this study are compared with those of other studies evaluating the SCS in NSCLC cohorts in Table 4.

Table 3. Patient-, Disease-, and Treatment-Related Risk Factors for Mortality—Univariate Analyses and Multivariate Analyses Adjusted for Male Sex, Age Older Than 75 Years, ECOG PS of 2 or Higher, Loss of Weight Greater Than 10%, and Stage Group

	Univariate			Multivariate		
	HR	95% CI	*p* Value[a]	HR	95% CI	*p* Value[a]
Patient factors						
Sex (male vs. female)	1.4	1.1-1.8	0.01	1.6	1.3-2.0	<0.01
Age (>75 y vs. ≤75 y)	1.3	1.0-1.6	0.04	1.5	1.1-1.9	<0.01
SCS (continuous)	1.1	1.0-1.1	<0.01	1.1	1.0-1.1	<0.01
SCS (> 9 vs. ≤9)	1.0	0.8-1.3	0.79	1.0	0.7-1.3	0.78
Alcoholism (yes vs. no)	0.7	0.5-1.2	0.21	0.9	0.5-1.4	0.54
Renal (yes vs. no)	1.6	1.1-2.5	0.02	1.2	0.8-1.9	0.38
Diabetes (yes vs. no)	1.1	0.9-1.5	0.36	1.1	0.8-1.4	0.61
Cardiovascular (yes vs. no)	1.2	1.0-1.5	0.09	1.1	0.8-1.4	0.59
Respiratory (yes vs. no)	1.2	1.0-1.5	0.11	1.7	1.4-2.1	<0.01
Neoplastic (yes vs. no)	0.9	0.7-1.1	0.40	1.1	0.9-1.4	0.41
ECOG PS (vs. ECOG PS = 0)	1.0			1.0		
ECOG PS = 1	1.6	1.2-2.2	<0.01	1.3	1.0-1.9	0.08
ECOG PS = 2	2.7	1.8-4.0	<0.01	2.2	1.5-3.2	<0.01
ECOG PS = 3	5.3	3.4-8.4	<0.01	3.7	2.3-6.0	<0.01
ECOG PS (≥2 vs. <2)	2.2	1.7-2.8	<0.01	2.0	1.6-2.6	<0.01
LOW at diagnosis (vs. 0%-10%)	1.0			1.0		
LOW 11%-15%	1.7	1.3-2.2	<0.01	1.4	1.0-1.8	0.04
LOW >15%	2.8	1.9-4.3	<0.01	1.9	1.2-2.9	0.01
LOW >10%	1.9	1.5-2.4	<0.01	1.5	1.4-1.9	<0.01
Smoking history (vs. never)	1.0			1.0		
Ever-smoker	2.3	1.5-3.4	<0.01	2.8	1.9-4.0	<0.01
Past smoker	2.1	1.5-3.0	<0.01	3.1	2.0-4.6	<0.01
Current smoker	2.2	1.5-3.1	<0.01	2.8	1.9-4.0	<0.01
Pack-years (continuous)	1.0	1.0-1.0	0.20	1.0	1.0-1.0	0.71
Pack-years (>median)	0.8	0.7-1.0	0.10	0.9	0.7-1.2	0.56
Pack-years (>75th percentile)	0.8	0.6-1.1	0.15	0.9	0.7-1.2	0.55
Years since smoking cessation						
≤1 y vs. >1 y	0.6	0.4-0.8	0.87	0.8	0.6-1.1	0.34
≤1 y vs. >10 y	0.5	0.3-0.7	0.95	0.7	0.5-1.0	0.28
Disease factors						
Stage (vs. stage I)	1.0			1.0		
Stage II	1.8	1.0-3.4	0.05	1.9	1.0-3.5	0.04
Stage IIIA	3.1	1.9-5.1	<0.01	3.3	2.0-5.4	<0.01
Stage IIIB	4.9	2.9-8.1	<0.01	5.6	3.3-9.4	<0.01
Stage IV	6.0	3.9-9.3	<0.01	7.2	4.6-11.2	<0.01
Metastatic vs. nonmetastatic	2.5	2.1-3.2	<0.01	2.8	2.3-3.5	<0.01
Nonadeno vs. adeno histological findings	1.5	1.2-1.8	<0.01	1.8	1.5-2.3	<0.01
Treatment factors[b]						
Curative surgery	0.2	0.2-0.4	<0.01	0.5	0.3-0.7	<0.01
Curative chemoradiotherapy	0.6	0.5-0.8	<0.01	0.8	0.6-1.1	0.13
Curative radiotherapy	0.4	0.3-0.7	<0.01	0.7	0.5-1.1	0.16
Chemotherapy[c]	1.0	0.8-1.2	0.92	0.8	0.6-1.0	0.03
Biologic therapy	0.6	0.5-0.8	<0.01	0.4	0.3-0.5	<0.01

[a] *p* Value for the comparison of overall survival for patients with and without the specified factor or as compared with that for patients in the specified factor reference group.
[b] Hazard ratio calculated for patients with specified treatment compared with for those without the specified treatment (i.e., curative surgery versus no curative surgery).
[c] Other than combined modality chemoradiotherapy and excluding biologic therapies.
HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern European Cooperative Group performance status; LOW, loss of weight; SCS, Simplified Comorbidity Score; adeno, adenocarcinoma.

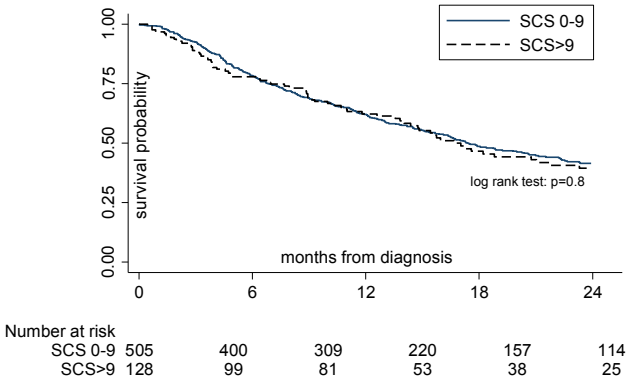

Figure 1. Unadjusted Kaplan-Meier survival estimate according to the Simplified Comorbidity Score (SCS).

Discussion

This study investigated whether comorbidity and the derived SCS were able to predict overall survival in a population of patients with NSCLC. Despite the high prevalence of comorbidity, neither comorbidity nor the derived SCS was a clinically significant predictor of mortality. In this cohort the most significant factors associated with mortality were smoking status, increased age, poor performance status, male sex, and advanced stage; any effect of SCS was accounted for by smoking history.

The studies evaluating the prognostic ability of the SCS in NSCLC to date have reported discordant findings.[2–5] Notably, three of the four most recent studies published since 2011 (including our own) demonstrated no prognostic significance of the SCS (>9 versus ≤9).[2,5] Furthermore, like Wang et al. who recently compared several multiparameter NSCLC prognostic models with performance status,[31] we found little or no advantage of the multiparameter SCS relative to performance status alone.

Discordant performance of the SCS across populations may, in part, reflect variation in data acquisition, comorbidity profile, and size of the cohort studies (Table 4). In our study, comorbidity was prospectively assessed by the study coordinator and validated by the treating clinician. However, specific details of data acquisition for many studies, such as whether it was achieved by real-time assessment, from medical records, or from health-coding data sets, is often unclear. Inherent biases in studies as a consequence of variation in data capture can be problematic for prognostic modeling (Alexander et al., unpublished data). Moreover, among studies evaluating the SCS in NSCLC, variation in comorbidity profile is evident (Table 4). Relative to the SCS derivation cohort,[3] our cohort was older and it was characterized by lower prevalence of respiratory comorbidity, cardiovascular comorbidity, and alcoholism and increased prevalence of diabetes and neoplastic comorbidity. The higher prevalence of past or concomitant neoplastic comorbidity may be explained by the older age of this cohort[32] or by selection bias at a cancer center compared with at a general hospital. The apparent lower prevalence of cardiovascular comorbidity in our cohort was explained by definition variation. Unlike within the SCS derivation cohort, hypertension was not defined as cardiovascular disease in the absence of end-organ dysfunction or other symptoms. Subsequent medical record review found that when hypertension was included, prevalence increased to 47%, which more closely aligned with that in other cohorts. Interestingly, the prognostic significance of hypertension (and other cardiovascular comorbidities) in lung cancer has been explored by Kravchenko et al. with varied effects across different populations (i.e., different effects for different stage and treatment groups).[33]

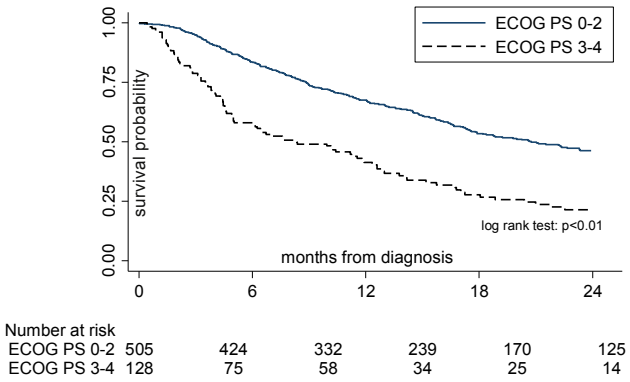

Figure 2. Unadjusted Kaplan-Meier survival estimate according to Eastern Cooperative Oncology Group performance status (ECOG PS).

Overall, our study had fewer patients with an SCS higher than 9 compared with other cohorts used in evaluating the SCS: 21% versus 33% to 47%.[3–5] Notwithstanding the small study population (n = 83), however, Girones et al. also found no prognostic effect of SCS in a cohort with 47% of patients recording a SCS higher than 9[5] and equally suggested that total comorbidity burden does not appear to be driving the predictive ability of the SCS.

Smoking history (past or current) is the most heavily weighted comorbidity in the SCS (7 points). With this weighting and a threshold of 9, comorbidities other than smoking have minimal impact on the overall SCS. For ever-smokers, this weighting rendered 65% of patients all scoring an SCS of 7 to 9. For never-smokers, however, the dichotomized SCS model became completely redundant, with patients requiring substantial or nearly all of the assessable comorbidities to reach the threshold of higher than 9 (not reached by any patient in this study). Never-smokers represented 15% of our cohort, which is

Table 4. Summary of Findings Related to the SCS in Various NSCLC Cohort Studies

	Author, Year of Publication				
	Alexander, 2016[a]	Ball, 2013[2]	Girones, 2011[5]	Jacot, 2008[4]	Colinet, 2005[3]
Study characteristics					
Cohort	NSCLC	NSCLC/SCLC	NSCLC/SCLC	NSCLC	NSCLC
Cohort size	633	655	83	301	871
Study design	Prospective	Retrospective	Prospective	Prospective	Prospective
Study follow-up	Median 17 mo	At least 5 y	At least 1 y	Median 21 mo	Median 26 mo
Population characteristics					
Median age, y	67 y	72 y	77 y	63 y	63 y
Male sex, %	63	63	98	80	80
ECOG PS ≥2	20	33	30	27	17
Alcoholism, %	7	6	NR	28	15
Cardiovascular comorbidity, %	27[b]	55	65	36	36
Diabetes mellitus, %	14	12	NR	12	9
Neoplastic comorbidity, %	26	20	NR	16	12
Renal insufficiency, %	5	5	NR	17	NR
Respiratory comorbidity, %	34	39	59	61	44
Tobacco, ever-smoker, %	86	83	95	92	87
Median SCS (range)	8 (0-19)	NR	9 (4-19)	NR	NR
SCS, % >9	20	NR	47	33	35%[c]
Survival outcomes					
Median overall survival	21 mo	6 mo	12 mo	17 mo	13 mo
1-y overall survival	62	31	NR	59	51
2-y overall survival	41	NR	NR	29	29
SCS and survival					
SCS >9 vs. ≤9, HR, 95% CI	1.0, 0.7-1.3	NSCLC: NR, $p = 0.08$	NR	1.8, 1.2-2.6	1.4, 1.1-1.7
SCC >9 predictive of mortality	No	No	No	Yes	Yes

[a]Alexander, 2016 refers to this article.
[b]Prevalence of 27% in the Thoracic Malignancies Cohort study, in which patients with hypertension were not recorded as having cardiovascular disease in the absence of other cardiovascular symptoms, and prevalence of 47% as defined according to the SCS definition and including hypertension.
[c]Validation cohort (n = 136) not reported for development cohort.
ECOG PS, Eastern European Cooperative Group Performance Status; NSCLC, non-small cell lung cancer; NR, not reported; SCLC, small cell lung cancer; SCS, Simplified Comorbidity Score.

consistent with population estimates of 10% to 15%,[34] but perhaps slightly higher than that observed by Ball et al.[2] (8%) and Colinet et al.[3] (9%). Importantly, population data from a French study suggest that the trend will be that of an increase in the proportion of never-smokers with lung cancer (10.9% in 2010 versus 7.2% in 2000).[35] Whether these trends reflect an increasing incidence of lung cancer among never-smokers or an increasing prevalence of never-smokers in the general population,[36] the changing distribution will have implications for the current SCS. In our cohort, among never-smokers, continuous SCS (HR per single SCS point = 1.2, 95% CI: 1.0–1.4, $p = 0.04$) and SCS higher than 1 versus 1 or lower (HR = 2.6, 95% CI: 1.04–6.29, $p = 0.04$) were predictive of mortality. As such, review and refinement of the contributors to a SCS, with appropriate weighting of these contributors based on frequency and potency, may allow the development of a more applicable and relevant comorbidity index that can be suitably applied across populations (i.e., smokers and never-smokers).

Diabetes, the second most heavily weighted comorbidity in the SCS (5 points), was relatively uncommon in our cohort (14%), with no impact on mortality ($p = 0.6$). Adverse outcomes may be more relevant to diabetic patients with risk factors such as poor overall diabetic control, increased age, and end-organ dysfunction. Accordingly, in a study of males with type 2 diabetes who were aged 55, 65, and 75 years, the estimated life expectancies (presented as a range for low- to high-risk factors) were 13 to 21 years, 8 to 15 years, and 4 to 10 years, respectively.[37] As such, the allocation of a single weighted score for the mere presence of diabetes, so heterogonous a chronic illness with reasonable long-term survival, in an NSCLC population with poorer short-term prognosis lacks potency and relevance.

Renal insufficiency, the third most heavily weighted comorbidity in the SCS (4 points) was rare in our cohort (5%), which did however shift 19 of 32 patients (59%) from low risk (SCS ≤9) to high risk (SCS >9) but had no impact on survival prediction.

The remaining contributors to the SCS are equally and weakly weighted (1 point). Alcoholism was rare in our cohort (6%) and had no impact on survival prediction. Cardiovascular comorbidity (27% or 47% depending on definition) and neoplastic comorbidity (26%) were common, yet still did not individually predict mortality. Only respiratory comorbidity demonstrated a relevant frequency (34%) and potency (HR = 1.7) to predict mortality ($p < 0.01$). Overall, the results for individual comorbidity indicate, comparably to the results of other studies,[10,15,22] that although the presence of comorbidity may contribute prognostically to the outcome of an individual patient, individual comorbid disease states per se do not provide adequate risk stratification across cohorts—which forms the fundamental driver for developing (weighted) comorbidity risk scores, such as the CCI or SCS.

There are a number of important factors that may affect our findings when compared with those of other lung cancer population studies. The observed 1-year survival rate of 62% in our cohort exceeds the population rates of 30% to 46%[38] and the rates in the study by Colinet et al. (51%)[3] and the study by Ball et al. (31%)[2] for patients with NSCLC and SCLC. This may reflect biases of this study population that was from a tertiary referral cancer specialist center and more likely to receive definite therapy. Moreover, survival did decrease with advancing stage, but only with a relatively small decline from stage IIIB (13 months) to stage IV (10 months). This comparatively improved survival of patients with stage IV disease may in part be a consequence of the proportion of patients with an actionable mutation (24%). In particular, 10% of our cohort had an epidermal growth factor receptor gene (*EGFR*) mutation compared with the expected population prevalence of approximately 5%;[39] the prevalence of anaplastic lymphoma kinase gene (*ALK*) and B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*) mutations aligned with the general population rates.[40–42] Equally, this study reports all-cause survival only, not disease-specific survival. Comorbidity as a predictor of survival may become pertinent only beyond the primary therapy and in longer-term survivors of lung cancer. The relatively short follow-up duration of this study (21 months in main cohort and 29 months in the cohort diagnosed in or before 2013) is a potential limitation of this study; however, Ball et al. also demonstrated no association between the SCS and survival with a minimum follow-up of 5 years.[2] To truly appreciate the contribution of non–cancer-specific comorbidity versus cancer-specific survival and the relevance of the SCS, future larger prospective studies, with systematic definitions and recording measures are required.

Risk stratification and predictive modeling tools can be important enablers for patients with longer-term conditions (or longer-term survivors) and can facilitate the design of better-targeted services and management strategies to improve patient outcomes. Of note, in our and other studies, basic and easy-to-measure patient variables, such as smoking status, sex, age, ECOG PS, LOW, and stage, did have a prognostic influence. The combination of these factors, together with disease- and treatment-related factors and, perhaps, simple relevant laboratory measures such as utilized in the modified Khorana risk scores for thromboembolism,[43,44] may provide better stratification and prognostication. Further, the role of comorbidity and other prognostic variables may have impacts that differ for different NSCLC populations, such as demonstrated among never-smokers in this cohort, but may also be relevant by disease stage or treatment strategy, which should be considered during derivation and validation of future prognostic models.

Acknowledgments

Ms. Alexander is a PhD student and was supported by the Australian Postgraduate Award from the Department of Epidemiology and Preventative Medicine, Monash University. The authors would like thank all the patients who participated in and continue to participate in the Peter MacCallum Cancer Centre Thoracic Malignancies Cohort Study.

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