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ORIGINAL ARTICLE

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The age-adjusted Charlson comorbidity index is a better predictor of survival in operated lung cancer patients than the Charlson and Elixhauser comorbidity indices

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Abstract

OBJECTIVES: To compare the prognostic performance between different comorbidity assessments of survival in patients with operated lung cancer.

METHODS: A total of 4508 lung cancer patients treated by surgery between 2003 and 2012 were identified through Taiwan's National Health Insurance Research Database. Information on pre-existing comorbidities prior to the cancer diagnosis was obtained and adapted to the Charlson comorbidity index, age-adjusted Charlson comorbidity index (ACCI) and Elixhauser comorbidity index scores. The influence on survival was analysed using a Cox proportional hazard model. The discriminatory ability of the comorbidity indices were evaluated using Akaike information criterion and Harrell's C-statistic.

RESULTS: The mean age of the study cohort was 64.95 ± 11.15 years, and 56.28% of the patients were male. The median follow-up time was 2.59 years, and the 3-year overall survival was 73.94%. Among these patients, 2134 (47.3%) patients received adjuvant therapy. The Charlson comorbidity index and ACCI scores correlated well with survival and higher scores were associated with an increased 3-year mortality risk (hazard ratio = 1.21, 95% confidence interval = 1.03–1.42 and hazard ratio = 1.43, 95% confidence interval = 1.08–1.90, respectively) in multivariate analysis. The ACCI scores provided better discriminatory ability with a smaller Akaike information criterion and greater Harrell's C-statistic for 3-year overall survival compared to the Charlson comorbidity index or Elixhauser comorbidity index scores.

CONCLUSIONS: The operated lung cancer patients with severe comorbidities were associated with worse survival. The ACCI appears to be a more appropriate prognostic indicator and should be considered for use in clinical practice.

Keywords: Lung cancer • Surgery • Charlson comorbidity index • Elixhauser comorbidity index • age • survival

INTRODUCTION

Lung cancer is the leading cause of cancer death worldwide and continues to be the most common cause of cancer deaths in Taiwan [1, 2]. The management of patients with lung cancer continues to be a challenge because the prognosis of these patients has remained poor over the last decade. Surgical resection for lung cancer patients, especially non-small-cell lung cancer (NSCLC), results in the most favourable survival outcome, but only 20% of patients are eligible for resection at the time of diagnosis [3]. Moreover, survival is dependent on not only tumour stage but also other factors, such as performance status, age or comorbidities. In addition to age and cigarette smoking, lung cancer patients have been shown to have a higher prevalence of comorbidities, such as cardiovascular disease, chronic pulmonary disease and other systemic diseases. The presence of

comorbidities is known to be a negative prognostic factor for survival in NSCLC patients [4]. Although lung cancer patients with severe comorbid conditions are excluded before surgery, mild or well-controlled coexisting comorbidities may still complicate treatment and diminish the treatment outcomes.

It is difficult to evaluate the impact of comorbidities at the same time and integrate these information into clinical practice and estimation of morbidity and mortality. Therefore, several measurements have been designed to evaluate and grade the degree of comorbidity burden such as Charlson comorbidity index (CCI) [5] and Elixhauser comorbidity index (ECI) [6]. The CCI score was first developed in 1984 by reviewing hospital charts to assess 1-year mortality and validated in a cohort of 685 breast cancer patients. Each diagnosis from 19 medical conditions was assigned a weighting score, and the index was the summation of all scores. Since then, the CCI score has become the most widely used clinical index for a variety of disorders and cancers [7–9]. Because age has been determined to influence survival, the CCI was modified by Charlson *et al.* [5] in 1994. This modification, the age-adjusted Charlson comorbidity index (ACCI), includes the age of the patient as a correction variable of the final score of the Charlson index. Another comorbidity assessment introduced by Elixhauser *et al.* [6, 10] was based on 30 different comorbid conditions and used to predict in-hospital mortality. The Elixhauser method has been utilized in many studies and is reliable as a prognostic factor in a number of cancers [11, 12]. However, the use of the Elixhauser comorbidity index (ECI) score has not been examined in a lung cancer patient setting. There is also no standard method that exists for assessing comorbidities in lung cancer patients postoperatively. Thus, it is important to identify the optimal method by which to predict outcome.

The primary aim of this study was to investigate the incidence of comorbidities and the impact on prognosis in a cohort of operated lung cancer patients. Furthermore, we compared these 3 comorbidity indices (CCI, ACCI or ECI score) to determine which one is a better survival predictor.

MATERIALS AND METHODS

Database and patient demographics

The population data were obtained from the National Health Insurance Research database (NHIRD), which was implemented in March 1995 and enrolled up to 99% of the Taiwanese population [13]. The database contains comprehensive information on all insured individuals, including diagnosis, age, gender, cancer type, comorbid diseases, socio-economic status, treatment rendered, medication use and death. Information on tobacco use, dietary habits and body mass index were not included in this database. The database contains a registry of contracted medical facilities, a registry of board-certified physicians and monthly medical insurance claims summaries for all inpatient claims. Patients with newly diagnosed lung cancer who underwent radical surgery with or without adjuvant therapy were included in this analysis. Patients who received neoadjuvant therapy were excluded. Finally, after excluding the patients with missing data, a total of 4508 patients were included in this study (Fig. 1). International Classification of Diseases (ninth revision, Clinical Modification) codes were used to obtain cancer diagnoses and comorbid conditions. The definition of diagnoses for comorbidities was recorded prior to lung cancer surgery.

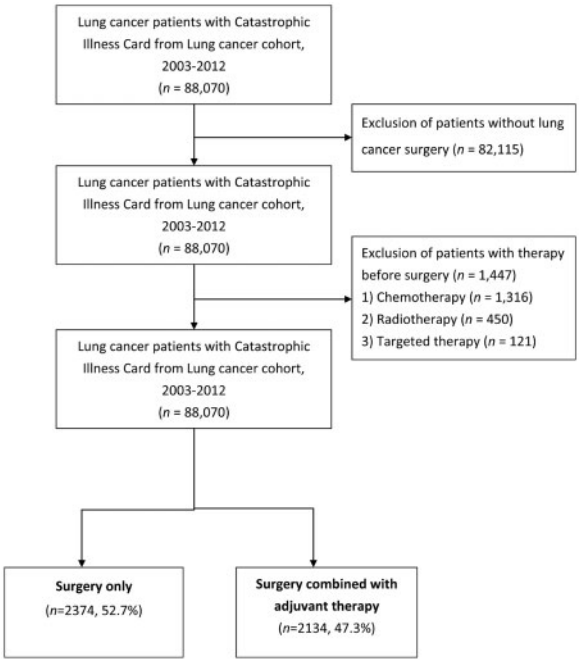

Figure 1: Patient selection flow chart.

This study was approved by the Institutional Review Board of Chi-Mei Medical Center in Taiwan (IRB: 10409-E02). The review board requirements for written informed consent were waived because all personal identifying information was removed from the data set prior to analysis.

Comorbidity assessment

The comorbidity assessment was performed using the following indices: (i) CCI, (ii) ACCI and (iii) ECI scores. The CCI score included 19 different medical conditions and each comorbid condition ranges from 1 to 6 points to sum an index score. The ACCI scores were calculated with additional points added for age. Each decade over the age of 40 years was assigned a comorbidity score of 1 [14]. The ECI scores were identified by separately summing scores in 30 different comorbid conditions as mentioned in previous literature [10, 15].

Statistical analysis

The different comorbid conditions were calculated for lung cancer patients undergoing major surgery with or without adjuvant therapy, and the main dependent variable, 3-year overall survival rate (OS), was also estimated. The definition of death was based on the death record from the inpatient claim data set, the sudden death unknown causes [International Classification of Diseases (ninth revision, Clinical Modification): 798] in the emergency department from the outpatient claim data set or withdrawal from the insurance programme without re-enrolment in the insurance health system. In this data set, disease-specific survival rates could not be determined. Roohan *et al.* [16] supported the opinion that there is no significant difference between survival models for all-cause and cancer-specific mortality. The overall survival curve was plotted using the Kaplan–Meier method and the difference between groups was compared using the log-rank

Table 1: Baseline characteristics ($n = 4508$)

Characteristics	Overall ($n = 4508$)	Surgery only ($n = 2374$)	Surgery combined with adjuvant therapy ($n = 2134$)	*P*-value
	n (%)	*n* (%)	*n* (%)	
Age at entry/surgery, years (mean ± SD)	64.95 ± 11.15	66.75 ± 10.98	62.95 ± 11.01	<0.0001
<40	81 (1.80)	30 (1.26)	51 (2.39)	<0.0001
40–49	392 (8.70)	157 (6.61)	235 (11.01)	
50–59	971 (21.54)	442 (18.62)	529 (24.79)	
60–69	1380 (30.61)	683 (28.77)	697 (32.66)	
70–79	1380 (30.61)	856 (36.06)	524 (24.55)	
≥80	304 (6.74)	206 (8.68)	98 (4.59)	
Gender				
Female	1971 (43.72)	1092 (46.00)	879 (41.19)	0.0012
Male	2537 (56.28)	1282 (54.00)	1255 (58.81)	
ECI (mean ± SD)	3.37 ± 5.26	3.62 ± 5.45	3.10 ± 5.01	0.0009
<0	149 (3.31)	75 (3.16)	74 (3.47)	0.0227
0	2315 (51.35)	1171 (49.33)	1144 (53.61)	
1–4	883 (19.59)	487 (20.51)	396 (18.56)	
≥5	1161 (25.75)	641 (27.00)	520 (24.37)	
CCI (mean ± SD)	1.23 ± 1.53	1.33 ± 1.59	1.12 ± 1.47	<0.0001
0	1887 (41.86)	911 (38.37)	976 (45.74)	<0.0001
1	1183 (26.24)	631 (26.58)	552 (25.87)	
2	671 (14.88)	399 (16.81)	272 (12.75)	
≥3	767 (17.01)	433 (18.24)	334 (15.65)	
ACCI (mean ± SD)	4.23 ± 2.13	4.51 ± 2.13	3.91 ± 2.09	<0.0001
≤2	949 (21.05)	400 (16.85)	549 (25.73)	<0.0001
3	809 (17.95)	366 (15.42)	443 (20.76)	
4	958 (21.25)	532 (22.41)	426 (19.96)	
≥5	1792 (39.75)	1076 (45.32)	716 (33.55)	
Treatment[a]				
Chemotherapy (yes/no)	1792 (39.75)	0 (0)	1792 (83.97)	<0.0001
Radiotherapy (yes/no)	847 (18.79)	0 (0)	847 (39.69)	<0.0001
Targeted therapy (yes/no)	343 (7.61)	0 (0)	343 (16.07)	<0.0001
Surgical methods				
Pneumonectomy (yes/no)	413 (9.16)	158 (6.66)	255 (11.95)	<0.0001
Bilobectomy (yes/no)	87 (1.93)	28 (1.18)	59 (2.76)	0.0001
Lobectomy (yes/no)	3287 (72.91)	1851 (77.97)	1436 (67.29)	<0.0001
Segmentectomy (yes/no)	132 (2.93)	64 (2.70)	68 (3.19)	0.3293
Wedge resection (yes/no)	1110 (24.62)	504 (21.23)	606 (28.40)	<0.0001
Three-year mortality	1175 (26.06)	374 (15.75)	801 (37.54)	<0.0001
Time to death, years [median (IQR)]	1.88 (0.90–3.39)	2.41 (0.78–4.07)	1.68 (0.92–3.00)	<0.0001
Follow-up time, years [median (IQR)]	2.59 (1.47–4.43)	2.95 (1.66–4.77)	2.28 (1.31–3.96)	<0.0001

ECI: Elixhauser comorbidity index; CCI: Charlson comorbidity index; ACCI: age-adjusted Charlson comorbidity index.
[a]After the surgery day within 1 year.

test. Cox proportional hazard analyses were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for survival of the different comorbid assessments. The impact of the CCI, ACCI and ECI scores on improvement of discrimination was examined by multivariable Cox regression model using the base model (age, gender, surgical methods and adjuvant therapy) plus each index scores alone. A discrimination analysis was performed to compare the predictive ability of the model against the base model (age, gender, surgical methods and adjuvant therapy) using the change in Harrell's C-statistic and the Akaike information criterion (AIC) [17]. The Harrell's C-statistic indicates model prediction as follows: 0.5 (as well as chance), 0.7–0.8 (acceptable), 0.8–0.9 (excellent) and 0.9–1 (outstanding prediction). The AIC statistic was calculated, and a small AIC indicates better prediction of the model. All statistical analyses were performed with SAS 9.4 for Windows (SAS Institute, Inc., Cary, NC, USA), and Kaplan–Meier curves were plotted from STATA (version 12; Stata Corp., College Station, TX, USA). A *P*-value <0.05 was considered significant.

RESULTS

A total of 4508 lung cancer patients post major surgery with or without adjuvant therapy were enrolled in this study [2537 men and 1971 women (ratio = 1.28:1)]. Table 1 presents the demographic characteristics of the study population. The median follow-up time was 2.59 years. The mean age was 64.95 ± 11.15 years, and 67.96% were ≥60 years. After surgery, 1792 patients (39.75%) underwent adjuvant chemotherapy and 847 patients (18.79%) received adjuvant radiotherapy.

The distribution of comorbidities based on the CCI and ECI methods is presented in Supplementary Material, Tables S1 and S2. Using the CCI, a total of 1887 patients (41.86%) had no comorbidity descriptor. The most common comorbid conditions were chronic pulmonary disease (23.8%), peptic ulcer disease (16.48%) and diabetes mellitus (15.75%). In contrast, by utilizing the ECI, the most common comorbid conditions were hypertension (40.2%), chronic pulmonary disease (23.78%) and diabetes mellitus (15.55%).

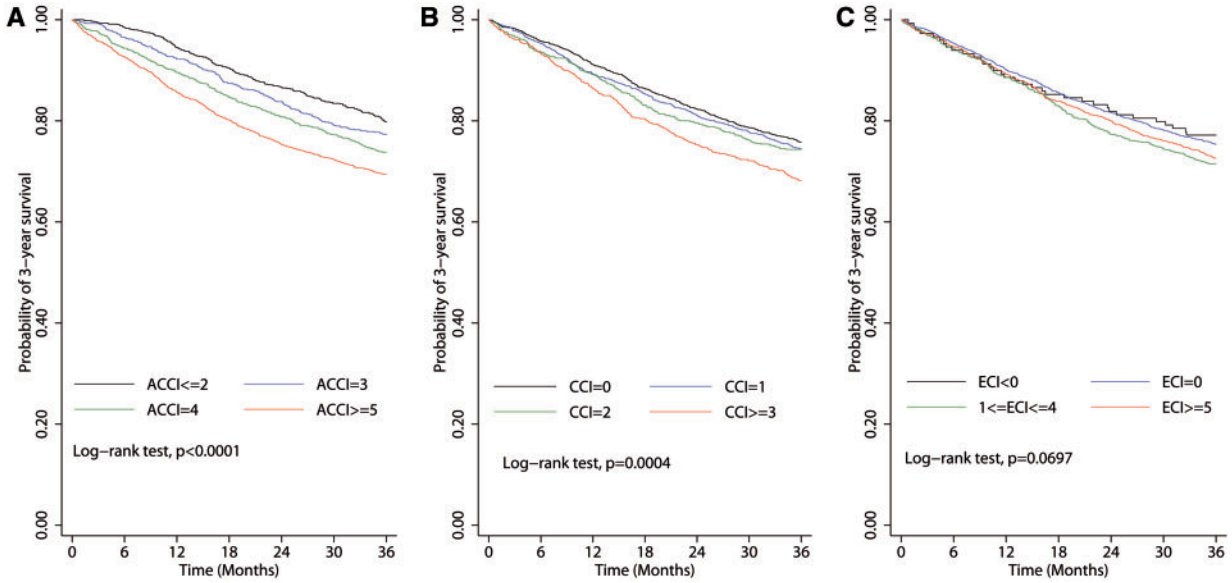

Figure 2: The impact of comorbidity on 3-year overall survival. (**A**) ACCI, (**B**) CCI and (**C**) ECI scores. ACCI: age-adjusted Charlson comorbidity index; CCI: Charlson comorbidity index; ECI: Elixhauser comorbidity index.

Table 2: Adjusted hazard ratios of 3-year mortality among lung cancer patients (2003–2012)

Characteristics	Overall (n = 4508)						Surgery only (n = 2374)			Surgery combined with adjuvant therapy (n = 2134)		
	Univariate analysis			Multivariable analysis[a]			Multivariable analysis[a]			Multivariable analysis[a]		
	HR	95% CI	P-value	aHR	95% CI	P-value	aHR	95% CI	P-value	aHR	95% CI	P-value
ECI model												
<0	1.00			1.00			1.00			1.00		
0	1.08	(0.76–1.53)	0.6651	0.95	(0.67–1.35)	0.7812	0.77	(0.43–1.36)	0.3606	1.11	(0.71–1.73)	0.6492
1–4	1.28	(0.90–1.84)	0.1709	0.98	(0.68–1.41)	0.9169	0.83	(0.46–1.49)	0.5210	1.15	(0.73–1.82)	0.5479
≥5	1.22	(0.86–1.74)	0.2744	1.01	(0.71–1.45)	0.9451	0.85	(0.48–1.52)	0.5923	1.16	(0.73–1.82)	0.5317
CCI model												
0	1.00			1.00			1.00			1.00		
1	1.07	(0.92–1.24)	0.3754	1.02	(0.88–1.18)	0.7950	0.96	(0.73–1.27)	0.7856	1.07	(0.90–1.28)	0.4440
2	1.09	(0.91–1.30)	0.3452	1.03	(0.86–1.23)	0.7518	1.04	(0.77–1.42)	0.7867	1.06	(0.85–1.33)	0.5951
≥3	**1.40**	**(1.20–1.63)**	**<0.0001**	**1.21**	**(1.03–1.42)**	**0.0225**	1.30	(0.99–1.71)	0.0631	1.19	(0.97–1.46)	0.0887
ACCI model												
≤2	1.00			1.00			1.00			1.00		
3	1.16	(0.95–1.42)	0.1595	1.14	(0.88–1.48)	0.3385	1.33	(0.69–2.58)	0.3923	1.10	(0.83–1.47)	0.5009
4	**1.37**	**(1.14–1.65)**	**0.0010**	1.28	(0.96–1.69)	0.0887	**1.93**	**(1.01–3.68)**	**0.0457**	1.18	(0.86–1.62)	0.3024
≥5	**1.67**	**(1.42–1.97)**	**<0.0001**	**1.43**	**(1.08–1.90)**	**0.0125**	**2.07**	**(1.09–3.96)**	**0.0267**	1.36	(0.99–1.86)	0.0594

The boldface value means statistical significant

ECI: Elixhauser comorbidity index; CCI: Charlson comorbidity index; ACCI: age-adjusted Charlson comorbidity index; HR: hazard ratio; CI: confidence interval; aHR: adjusted hazard ratio.

[a]Adjusted for the patients' age, gender, surgical methods and postoperative adjuvant therapy, including chemotherapy, radiotherapy and targeted therapy.

The 3-year OS according to different comorbidity indices (CCI, ACCI and ECI scores) is shown in Fig. 2. Higher CCI and ACCI scores were associated with a poor 3-year OS (P < 0.0001). Thus, the CCI and ACCI systems could be used to classify patients in prognostic groups according to comorbidities; however, there was no statistically significant difference in OS in the ECI group (P = 0.0697). Table 2 presents the HRs of mortality using CCI, ACCI and ECI scores among the study population, respectively. Multivariate analysis indicated that only increased CCI and ACCI scores were significantly associated with an increased mortality risk for 3-year OS (HR = 1.21, 95% CI = 1.03–1.42 and HR = 1.43, 95% CI = 1.08–1.90, respectively). In particular, different to the CCI and ECI score, the ACCI score remained an independent risk factor after adjusting for previous variables and adjuvant therapy (HR = 2.07, 95% CI = 1.09–3.96).

Table 3 presents the Harrell C-statistic and AIC for the CCI, ACCI and ECI methods adjusted for age, gender, surgical methods and adjuvant therapy for 3-year survival. All patients (n = 4508) were separated into 2 groups [surgery alone (n = 2374) and surgery with adjuvant therapy (n = 2134)]. Based on category analysis, the ACCI score was a better comprehensive comorbidity risk adjustment with a lower AIC (18 753.089) and higher C-statistic (0.7236) than the CCI or ECI scores for these operated lung cancer patients.

Table 3: Discrimination of 3-year survival estimation between ECI, CCI and ACCI among lung cancer patients

	Overall ($n = 4508$)		Surgery only ($n = 2374$)		Surgery combined with adjuvant therapy ($n = 2134$)	
	AIC	Harrell's C	AIC	Harrell's C	AIC	Harrell's C
Base model[a]	18 754.763	0.7219	5565.507	0.7052	11 665.162	0.6801
Using category						
Base model + ECI	18 759.988	0.7221	5570.184	0.7064	11 670.559	0.6802
Base model + CCI	18 755.100	0.7231	5566.626	0.7074	11 668.290	0.6810
Base model + ACCI	**18 753.089**	**0.7236**	**5564.748**	**0.7108**	**11 666.550**	**0.6815**

The boldface value means the model have the better discrimination.
ECI: Elixhauser comorbidity index; CCI: Charlson comorbidity index; ACCI: age-adjusted Charlson comorbidity index; AIC: Akaike's information criterion.
[a]Base model included age, gender, surgical methods and adjuvant therapy (chemotherapy, radiotherapy and targeted therapy).

DISCUSSION

In this population-based study for operated lung cancer patients, we observed that the comorbidity has a significant impact on survival. Apart from the ECI, CCI and ACCI severity correlated well with survival and can be used for therapeutic decision making; however, our analysis suggested that the ability to discriminate and accurately predict survival in operated lung cancer patients were statistically better with the ACCI, which adjusts for age.

Surgical resection is the most effective treatment for controlling disease in lung cancer patients, especially for NSCLC; however, only 20% of patients are eligible for resection and the 5-year survival following surgery is still disappointing [18]. As the mean age in lung cancer patients has increased due to a longer life expectancy, the coexisting comorbidities have been repeatedly evaluated as an important prognostic factor for survival [19, 20]. Patients with serious comorbidities are usually excluded from surgical management to prevent excessive morbidity and mortality. Thus, most of these patients have mild or medically well-controlled comorbid diseases, but these comorbidities increase the postoperative complications and adversely affect prognosis or are not amenable to adjuvant treatment [21]. Currently, there is no standard method for assessing comorbidities in lung cancer patients post-surgery. Thus, it is important to identify the optimal method with which to predict outcome.

Although several studies have demonstrated that the Elixhauser comorbidity measure is a better comorbidity risk adjustment system [11, 22–24], the Elixhauser comorbidity measure did not outperform the age-adjusted Charlson method in our study. One possible reason for this finding is that the Elixhauser method did not show better discrimination due to inclusion of a large number of explanatory variables. Too many variables may hamper convergence of the estimate based on multivariate analysis. Another reason for this finding is that the incidence of lung cancer increases with age; specifically, 60% of lung cancers arise in patients ≥60 years of age and 30% occur in patients ≥70 years of age [25]. Ageing is associated with comorbid conditions and increases treatment-related toxicities, which affect a patient's ability to tolerate cancer therapy [19, 20]. The mean age of the patients in the current study was 65 years, and >60% of patients were ≥60 years of age. Wang *et al.* [2] reported similar survival rates for patients <45 years of age and patients 46–64 years of age. Age >65 years at the time of diagnosis is an unfavourable prognostic factor in Taiwan. Furthermore, age and comorbid conditions independently influence patient selection for adjuvant modality therapy after curative resection.

An increase in comorbid conditions is associated with negative health outcomes in lung cancer patients [4, 20, 26]. In the current study, Charlson comorbidity method was used to compare with ECI because it has been extensively used in a variety of cancer conditions, including lung cancer [18, 21]. Birim *et al.* [18] demonstrated that CCI is an independent factor that influences long-term outcomes in NSCLC patients. Among patients with a Charlson comorbidity grade of 1–2, the 5-year overall survival was 48% (95% CI = 39–57), and among patients with a Charlson comorbidity grade of 3, the 5-year overall survival was 28% (95% CI = 18–38). Asmis *et al.* [19] retrospectively analysed more than 1200 patients and confirmed a relationship between age and comorbidity. Both age and comorbidities are associated with more severe toxicity and with a lower chemotherapy dose intensity. This finding indicates that the ACCI is a better predictor of survival than individual comorbid conditions and validates the ability of the ACCI to stratify comorbid severity in operated lung cancer patients.

Limitations

This study had several limitations. First, we could not assess the relationship between the comorbidity index and tumour stage because the staging information was not available from the database. Second, we included all lung cancer patients who underwent surgical resections. Although information on lung cancer subtypes was not provided in the NHIRD, most of these patients had NSCLC because small-cell lung cancer with surgical resection is recorded in only 1% of cases in the Taiwan Cancer Registry annual report [27]. Moreover, the tumour subtypes in NSCLC patients were not recorded in the NHIRD, yet the influence between adenocarcinoma and squamous cell carcinoma is controversial [28, 29]. Further studies linked to the Taiwan Cancer Registry database should be investigated. Third, personal habits, such as cigarette smoking and alcohol use, were not recorded in the NHIRD. Using a specific method designed for lung cancer, such as a simplified comorbidity score [30], may be helpful in the evaluation of comorbid conditions. Fourth, we analysed the association between different comorbidity indices and overall survival rates, not cancer-specific survival rates. Roohan *et al.* [16]

reported no significant difference between survival models for overall and cancer-specific survival rates in breast cancer patients. The basis for this finding may be because the dominant cause of death is cancer, and not a comorbid condition, among cancer patients.

CONCLUSION

The assessment of comorbid conditions is of great importance for lung cancer patients after surgical resection because comorbidity significantly affects survival. The ACCI score, which includes age, had better discrimination and predictive accuracy for prognosis compared with the CCI and ECI scores and could have widespread applicability.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

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