


ORIGINAL ARTICLE

Lung cancer outcome in the setting of chronic kidney disease: Does the glomerular filtration estimation formula matter?

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Keywords

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Abstract

Background: The survival outcomes of lung cancer patients with coexisting chronic kidney disease (CKD) reported in the literature have been conflicting. We evaluate whether the survival of lung cancer patients with and without CKD differ significantly using two different formulas.

Methods: A retrospective, multicenter, propensity-matched study of lung cancer patients with and without CKD was conducted. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/minute. Kaplan–Meier survival analysis was used to determine survival differences between CKD and non-CKD patients using the Cockcroft–Gault formula (CKD–CG) compared to the Chronic Kidney Disease Epidemiology Collaboration Formula (CKD–EPI).

Results: Baseline clinical characteristics did not differ statistically significantly between the groups. The CKD–CG formula demonstrated median survival of 10.61 months (95% confidence interval [CI] 9.33–11.89) for the non-CKD group compared to 10.58 months (95% CI 9.03–12.13) for the CKD group ($P = 0.76$). The CKD–EPI formula demonstrated median survival of 9.10 months (95% CI 8.01–10.20) for the non-CKD group compared to 7.59 months (95% CI 6.50–8.68) for the CKD group ($P = 0.19$). Cox regression analysis using both models revealed that CKD is not an independent risk factor for mortality in lung cancer patients. Although the CKD–EPI formula revealed an increased risk of mortality and the CKD–CG formula revealed decreased survival, these results were not statistically significant.

Conclusion: Lung cancer survival did not differ significantly between CKD and non-CKD patients using either formula.

Introduction

Lung cancer is the leading cause of cancer death worldwide.¹ In the United States, the age-adjusted mortality rate of lung cancer is 40.6 per 100 000 people, which is double the age-adjusted mortality of breast cancer at 20.3 per 100 000 people.² Recent technological and medical improvements have

contributed to longer life expectancy. However, the prevalence of chronic disease and cancer has increased with the global aging of the population. The initial cancer stage at the time of diagnosis usually determines survival prospects. However, the presence of a diversity of comorbidities will influence treatment planning and the effectiveness of such treatment.

Chronic kidney disease (CKD) markers account for 4.4% of overall cancer incidence and are responsible for 3.3 years of life lost.³ However, studies of survival outcomes of lung cancer patients with deteriorated renal function have shown conflicting results in the literature.^{4–8} In this study, we first evaluated survival outcomes of patients with lung cancer and coexisting CKD using a propensity-matched study using two commonly used formulas for estimating glomerular filtration rate. Second, we tested the hypothesis that CKD is an independent risk factor for mortality in patients with lung cancer.

Methods

We collected clinical data from three hospitals from the Chang Gung Medical Foundation (Kaohsiung Chang Gung Hospital, Chang Gung Memorial Hospital at Keelung, and Chang Gung Memorial Hospital at Chiayi). We included all adult patients (aged > 18 years) diagnosed with lung cancer from January 2007 to December 2012 in this retrospective study. Propensity score matching was used, with a 1:1 match of patients with lung cancer and coexisting CKD to patients with lung cancer without CKD based on age, gender, smoking status, comorbidity score, histology, and lung cancer stage. The creatinine level measured at the time of cancer diagnosis or clinical staging workup was used to calculate the estimated glomerular filtration rate (eGFR). An eGFR < 60 mL/minute/1.73 m² in the presence of proteinuria/hematuria or the presence of abnormal kidney imaging was used to define CKD; otherwise the sole presence of a creatinine eGFR < 60 mL/min/1.73 m² was considered non-CKD. CKD was staged according to current international guidelines.⁹

We used two different formulas to estimate GFR: the Cockcroft–Gault formula (CKD-CG)¹⁰ and the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).¹¹ Electronic medical records and cancer center databases at the respective hospitals were cross-matched to determine the coexistence of lung cancer and CKD. Clinical data extracted from the medical records included: age at diagnosis of lung cancer, gender, smoking history, creatinine level, cancer histology and stage at diagnosis, primary treatment received (all treatment modes administered within 3 months after diagnosis), Charlson comorbidity index (CCI)¹² and overall survival. The 19 chronic disease morbidity scores were added to calculate the CCI, which was used to determine an association between CKD and mortality. Lung cancer was staged according to the 7th edition of the tumor node metastasis (TNM) staging system for lung cancer.¹³ We excluded cases with incomplete medical records, incomplete cancer staging, or the absence of lung cancer pathology reports reconfirmed by our in-house pathologist. Overall survival (OS) was measured from the day of

pathology confirmation to the last follow-up or at the end of 2015, whichever came first. Patients lost to follow-up were contacted by telephone by the cancer center case manager, and those not reachable by telephone were presumed dead if they had withdrawn from National Health Insurance. National Health Insurance offers universal coverage to > 99% of the Taiwanese population. Patients are excluded from the scheme as a result of death, missing premium payments for > 6 months, emigration, or change of nationality. The Health Promotion Administration, Ministry of Health and Welfare, Taiwan, release an annual death report of all cancer cases registered back to each cancer center for a status update. The institutional review board of Chang Gung Memorial Hospital approved this study.

Statistical analysis

The propensity score was calculated using logistic regression with CKD as the dependent variable. Propensity matching was used to select control patients (CKD) who were similar to patients without CKD based on CKD-CG and CKD-EPI formulas. The matching process included several factors simultaneously (age, gender, smoking status, CCI score, lung cancer clinical staging, lung cancer history, and primary treatment).¹⁴ For matched pairing, we used a caliper width of 0.2 x the standard deviation of the propensity score without replacement.¹⁵

Comparisons of clinicopathological parameters among different groups were made using chi-square or Fisher's exact tests for categorical variables and analysis of variance for numerical variables. Continuous variables were categorized into a categorical variable using median values as the cutoff point. We divided clinical stage into stage I–IIIA versus IIIB–IV, and treatment modality into supportive treatment, surgical treatment (excluding diagnostic/staging procedure), and medical treatment groups. OS was assessed using the Kaplan–Meier method, and differences in survival were calculated using the log-rank test. Cox proportional hazard analysis was used to estimate the level of significance and the relative risks with 95% confidence intervals (CIs). A *P* value < 0.05 was considered significant. The clinical data were analyzed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 4323 lung cancer patients were included for analysis and 255 were excluded (our in-house pathologist confirmed no lung cancer in 168 patients, incomplete medical treatment records for 43 patients, incomplete lung cancer staging for 36 patients, and secondary pulmonary malignancy in 8 patients). The recruitment flow process is presented in the supplemental material.

Demography

Age, gender, smoking status, cancer histology, cancer stage, and the treatment received were not statistically significantly different between the CKD and non-CKD groups using either the CKD-CG or CKD-EPI formulas (Table 1).

CKD patients presented with higher CCI scores compared to non-CKD patients, regardless of the formula used (CKD-CG 8 vs. 7, $P = 0.007$ and CKD-EPI 9 vs. 8, $P = 0.03$). Table 2 summarizes the cancer histology types according to clinical cancer stage.

Table 1 Demographic characteristics of patients with CKD and non-CKD based on CKD-CG or CKD-EPI formula

Characteristics	CKD-CG			<i>P</i>	CKD-EPI			<i>P</i>
	Total (%)	Non-CKD	CKD		Total (%)	Non-CKD	CKD	
Number of patients	1668 (100)	834 (50)	834 (50)		1666 (100)	833 (50)	833 (50)	
Age (median + SD, years)	71 ± 9.42	71 ± 9.44	71 ± 9.40	0.08	75 ± 9.03	75 ± 8.87	75 ± 9.17	0.36
Gender				0.76				1.00
Female	551 (33)	272 (32.6)	279 (33.5)		518 (31.1)	259 (31.1)	259 (31.1)	
Male	1117 (67)	562 (67.4)	555 (66.5)		1148 (68.9)	574 (68.9)	574 (68.9)	
Smoking history				0.62				0.46
No	793 (47.5)	391 (46.9)	402 (48.2)		748 (44.9)	366 (43.9)	382 (45.9)	
Yes	875 (52.5)	443 (53.1)	432 (51.8)		918 (55.1)	467 (56.1)	451 (54.1)	
Creatinine (median + SD, mg/dL)	0.93 ± 0.96	0.79 ± 1.83	1.12 ± 1.25	< 0.001	1.10 ± 1.12	0.86 ± 0.39	1.4 ± 1.38	< 0.001
eGFR (median + SD, mL/min)	59.99 ± 23.63	75.33 ± 18.30	48.73 ± 12.81	< 0.001	59.95 ± 22.95	78.90 ± 12.95	47.40 ± 14.62	< 0.001
Comorbidity score (median + SD)	7 ± 2.53	7 ± 2.50	8 ± 2.56	0.007	9 ± 2.47	8 ± 2.50	9 ± 2.45	0.03
Lung cancer stage				1				0.31
IA–IIIA	377 (22.6)	188 (22.5)	189 (22.7)		366 (22.0)	192 (23.0)	174 (20.9)	
IA	71 (4.3)	34 (4.1)	37 (4.4)		53 (3.2)	27 (3.2)	26 (3.1)	
IB	94 (5.6)	48 (5.8)	46 (5.5)		94 (5.6)	51 (6.1)	43 (5.2)	
IIA	34 (2.0)	14 (1.7)	20 (2.4)		29 (1.7)	16 (1.9)	13 (1.6)	
IIB	29 (1.7)	17 (2.0)	12 (1.4)		29 (1.7)	14 (1.71)	15 (1.8)	
IIIA	149 (8.9)	75 (9.0)	74 (8.9)		161 (9.7)	84 (10.1)	77 (9.2)	
IIIB–IV	1555 (77.4)	777 (77.3)	778 (77.4)		1300 (78.0)	641 (77.0)	659 (79.1)	
IIIB	197 (11.8)	100 (12.0)	97 (11.6)		184 (11.0)	90 (10.8)	94 (11.3)	
IV	1094 (65.6)	546 (65.5)	548 (65.7)		1116 (67.0)	551 (66.1)	565 (67.8)	
Histology				0.80				0.54
NSCLC	1512 (90.6)	758 (90.9)	754 (90.4)		1479 (88.8)	744 (89.3)	735 (88.2)	
SCLC	156 (9.4)	76 (9.1)	80 (9.6)		187 (11.2)	89 (10.7)	98 (11.8)	
Treatment				0.27				0.40
No treatment/supportive care	289 (17.3)	132 (15.8)	157 (18.8)		421 (25.3)	200 (24.0)	221 (26.5)	
Surgical treatment	264 (15.8)	133 (15.9)	131 (15.7)		210 (12.6)	111 (13.3)	99 (11.9)	
OP	155 (9.3)	69 (8.3)	86 (10.3)		126 (7.6)	64 (7.7)	64 (7.4)	
OP + CT	81 (4.9)	45 (5.4)	36 (4.3)		67 (4.0)	38 (4.6)	29 (3.5)	
OP + RT	8 (0.5)	6 (0.7)	2 (0.2)		6 (0.4)	2 (0.2)	4 (0.5)	
OP + CT + RT	10 (0.6)	8 (1)	2 (0.2)		4 (0.2)	3 (0.4)	1 (0.1)	
OP + Target	9 (0.5)	3 (0.4)	6 (0.7)		5 (0.3)	1 (0.1)	4 (0.5)	
Medical treatment	1115 (66.8)	569 (68.2)	546 (65.5)		1035 (62.1)	522 (62.7)	513 (61.6)	
CT	538 (32.3)	277 (33.2)	261 (31.3)		481 (28.9)	232 (27.94)	249 (29.9)	
CT + RT	204 (12.2)	101 (13.2)	94 (11.3)		172 (10.3)	94 (11.3)	78 (9.4)	
CT + Target	35 (2.1)	20 (2.4)	15 (1.8)		41 (2.5)	23 (2.8)	18 (2.2)	
RT	85 (5.1)	49 (5.9)	36 (4.3)		98 (5.9)	57 (6.8)	41 (4.9)	
RT + Target	36 (1.7)	14 (1.8)	22 (2.6)		34 (2.0)	15 (1.8)	19 (2.3)	
Target	215 (12.9)	98 (11.8)	117 (14.0)		210 (12.6)	103 (12.4)	107 (12.8)	
Cryotherapy	2 (0.1)	2 (0.2)	0 (0)		1 (0.1)	1 (0.1)	0 (0)	

CKD, chronic kidney disease; CKD-CG, CKD-Cockcroft–Gault formula; CKD-EPI, CKD-Epidemiology Collaboration formula; CT, chemotherapy; NSCLC, non-small cell lung cancer; Op, surgical resection; RT, radiotherapy; SCLC, small cell lung cancer; Target, targeted therapy.

Treatment

The proportion of patients who received supportive treatment was slightly higher in the CKD compared to the non-CKD group (CKD-CG 18.8% vs. 15.8% and CKD-EPI 26.5% vs. 24%, respectively). The proportion of patients who received medical treatment was slightly higher in the non-CKD compared to the CKD group measured by CKD-CG (68.2% vs. 65.5%, respectively), while the proportion of patients who received surgical treatment was slightly higher in the non-CKD compared to the CKD group measured by CKD-EPI (13.3% vs. 11.9%, respectively) (Table 1).

Survival according to different chronic kidney disease (CK) formula

The OS rates were not statistically significantly different between the CKD and non-CKD groups using either the CKD-CG or the CKD-EPI formula. Using the CKD-CG formula, OS in the non-CKD group was 10.61 months (95% CI 9.33–11.89) and 10.58 months (95% CI 9.03–12.13) in the CKD group ($P = 0.76$) (Fig 1a). Using the CKD-EPI formula, OS in the non-CKD group was 9.10 months (95% CI 8.01–10.20) and 7.59 months (95% CI 6.50–8.68) in the CKD group ($P = 0.19$) (Fig 1b).

Non-CKD versus CKD survival

Age, gender, smoking status, cancer histology, cancer stage, and treatment received were not statistically different between the CKD and non-CKD groups according to either the CKD-CG or CKD-EPI formulas (Table 3). The survival rates by cancer stage of patients with and without CKD and according to the different CKD stages are presented in Table 4. Survival rates according to the different CKD stages in cancer stages IIIB–IV were statistically significantly different using the CKD-CG ($P = 0.004$) and CKD-EPI formulas ($P < 0.001$). However, survival in cancer stage IA–IIIA patients was statistically different using the CKD-CG formula ($P < 0.001$) and only marginally significant using the CKD-EPI formula ($P = 0.054$).

In the adjusted Cox proportional hazard analysis model, age, CCI score, cancer stage, cancer histology, and treatment mode were factors associated with increased mortality when measured by both formulas. Male patients had an increased risk of death when measured using the CKD-EPI formula (hazard ratio [HR] 1.24, 95% CI 1.07–1.43; $P = 0.01$) but the result did not reach statistical significance using the CKD-CG formula. Using an eGFR < 60 mL/minute/1.73 m² as an indicator of CKD, CKD patients presented with decreased survival when measured using the CKD-CG formula (HR 0.96, 95% CI 0.88–1.08;

Table 2 Cancer histology distribution according to cancer stage

Histology type	CKD-CG (n, %)					CKD-EPI (n, %)								
	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage IIIB	Stage IIIA	Stage IIIB	Stage IV	Total					
NSCLC	70 (98.6)	53 (98.9)	93 (100)	32 (94.1)	29 (100)	28 (96.6)	135 (90.6)	146 (90.7)	172 (87.3)	150 (81.5)	982 (89.8)	979 (87.7)	1512 (90.6)	1479 (88.8)
Adenocarcinoma	53	35	53	43	14	13	15	13	59	46	61	68	659	915 (54.9)
Squamous cell carcinoma	11	14	27	33	12	9	12	12	80	79	67	212	189	376 (22.5)
Adenosquamous cell carcinoma	1	8	7	3	1	1	7	4	8	7	4	26	22	50 (3)
Large cell carcinoma	1	3	6	0	1	0	7	5	6	5	7	23	12	29 (1.7)
Sarcomatoid carcinoma	0	1	3	0	0	1	4	3	2	1	3	17	14	22 (1.3)
Carcinoid tumor	2	0	0	0	0	1	0	0	0	0	0	1	2	5 (0.3)
Salivary gland tumours	0	0	0	0	0	0	1	0	1	0	0	0	1	3 (0.2)
NSCLC NOS	2	2	1	3	2	1	6	6	16	12	6	90	83	112 (6.7)
Other	0	0	0	0	0	0	0	0	0	0	0	2	0	2 (0.1)
SCLC	1 (1.4)	1 (1.1)	0 (0)	2 (5.9)	0 (0)	1 (3.4)	14 (9.4)	15 (9.3)	25 (12.7)	34 (18.5)	112 (10.2)	137 (12.3)	156 (9.4)	187 (11.2)

NSCLC, non-small cell lung cancer; NOS, not otherwise specified; SCLC, small cell lung cancer.

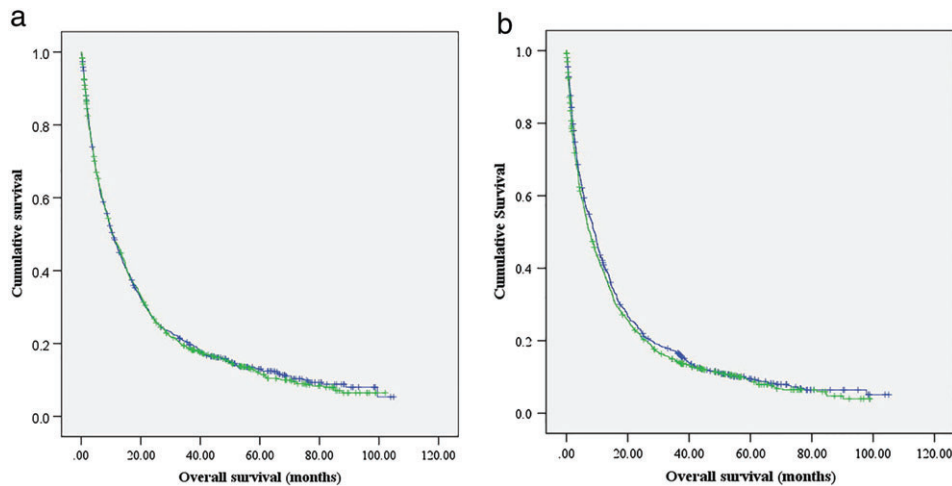


Figure 1 Survival curves of lung cancer with and without chronic kidney disease (CKD) according to the (a) CKD-Cockcroft-Gault (CKD-CG) and (b) CKD-Epidemiology Collaboration formulas. (—) CKD (-), (—) CKD (+), (+) CKD (-)-censored, and (+) CKD (+)-censored.

$P = 0.65$) and an increased risk of death when measured using the CKD-EPI formula (HR 1.05, 95% CI 0.95–1.17; $P = 0.33$), but these results did not reach statistical significance. With medical treatment as the reference, patients receiving supportive treatment had an increased risk of death according to both formulas, while those receiving surgical treatment had a decreased risk of death (Table 5).

Discussion

Patients with cancer are usually older in general, with a higher prevalence of comorbidities, such as CKD. The prevalence of CKD is high in the elderly, affecting > 40% of people over the age of 70 years.¹⁶ According to the National Health and Nutrition Examination Survey

Table 3 Kaplan–Meier survival analysis of non-CKD and CKD groups using the CKD-CG and CKD-EPI formulas

Characteristics	CKC-CG					CKD-EPI				
	Non-CKD		CKD		<i>P</i>	Non-CKD		CKD		<i>P</i>
	Median (months)	95% CI	Median (months)	95% CI		Median (months)	95% CI	Median (months)	95% CI	
Overall survival	10.61	9.33–11.89	10.58	9.03–12.13	0.76	9.10	8.01–1.20	7.59	6.50–8.68	0.19
Age					0.78					0.17
< median value	12.39	10.29–14.48	14.23	11.94–16.51	0.73	11.14	9.46–13.34	10.71	8.92–12.51	0.79
> median value	9.10	7.17–11.03	7.95	6.49–9.42	0.46	6.11	4.52–7.71	4.90	3.84–5.95	0.10
Gender					0.76					0.21
Female	13.50	10.61–16.39	15.11	11.70–18.52	0.39	13.73	11.23–16.24	9.23	6.77–11.69	0.66
Male	9.27	7.80–10.73	9.53	8.28–10.78	0.33	7.52	6.09–8.96	6.67	5.39–7.95	0.23
Smoking history					0.70					0.26
No	14.03	11.48–16.58	14.88	11.91–17.86	0.74	12.09	9.86–14.33	8.64	6.42–10.86	0.50
Yes	8.87	7.50–10.24	9.00	7.76–10.25	0.40	7.33	5.87–8.78	6.77	5.60–7.94	0.37
Comorbidity score					0.68					0.63
< median value	14.52	11.87–17.17	16.07	13.01–19.12	0.45	10.32	8.88–11.75	9.76	7.84–11.68	0.74
> median value	6.87	5.41–8.33	6.97	5.68–8.25	0.89	5.29	3.39–7.19	4.40	2.88–5.73	0.67
Stage					0.97					0.29
IA–IIIA	41.23	33.55–49.31	35.15	20.42–49.89	0.27	30.82	21.77–39.87	24.38	17.61–31.14	0.71
IIIB–IV	7.82	6.61–9.03	8.02	6.86–9.17	0.66	6.37	5.19–7.56	5.59	4.69–6.48	0.32
Histology					0.81					0.28
NSCLC	11.37	9.72–13.02	11.17	9.32–13.03	0.86	9.96	8.74–11.17	8.51	7.19–4.78	0.26
SCLC	6.21	4.41–8.01	5.75	3.27–8.23	0.82	4.70	3.97–5.42	3.29	1.79–4.73	0.91
Treatment					0.96					0.15
Supportive	2.73	1.15–4.30	2.40	1.47–3.33	0.59	2.79	2.18–3.41	1.64	1.02–2.26	0.04
Medical	9.13	7.85–10.42	10.02	8.54–11.50	0.66	9.43	8.32–10.54	8.64	7.14–10.14	0.57
Surgical	70.57	55.90–85.25	61.83	49.97–73.70	0.77	48.82	31.90–65.75	60.35	51.71–68.99	0.86

Overall survival was not statistically significantly different between the CKD and non-CKD groups using either the chronic kidney disease Cockcroft–Gault (CKD-CG) or CKD-Epidemiology Collaboration (CKD-EPI) formulas. CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Table 4 Survival by cancer stage according to the presence or absence of CKD and CKD stage

Cancer stage	Formula	Non-CKD			CKD 3A			CKD 3B			CKD 4			CKD 5			P
		N	Median (95% CI)	N	Median (95% CI)	N	Median (95% CI)	N	Median (95% CI)	N	Median (95% CI)	N	Median (95% CI)	N	Median (95% CI)		
IA–IIIA	CKD-CG	188	41.43 (33.55–49.31)	120	48.72 (30.42–67.03)	48	27.40 (12.36–42.44)	13	14.88 (0.00–34.91)	8	10.22 (0.00–32.57)	0.004					
	CKD-EPI	192	30.82 (21.77–39.87)	102	27.83 (11.40–44.25)	37	19.45 (8.17–30.73)	20	42.35 (8.06–76.64)	15	10.22 (0.00–22.26)	0.054					
IIIB–IV	CKD-CG	646	7.82 (6.61–9.03)	397	10.25 (8.53–11.97)	169	6.21 (4.55–7.87)	47	3.75 (2.99–4.50)	32	3.35 (0.54–6.16)	<0.001					
	CKD-EPI	641	6.37 (5.19–7.56)	366	6.77 (5.17–8.37)	162	4.01 (3.15–4.87)	83	4.57 (3.02–6.11)	48	3.35 (0.00–6.72)	<0.001					

The survival differences using the chronic kidney disease-Epidemiology Collaboration (CKD-EPI) formula were significant for cancer stage IIIB–IV ($P < 0.001$) but not for IA–IIIA ($P = 0.054$). CKD stage 3A (estimated glomerular filtration rate [eGFR] range 45–60 mL/min/1.73 m²), CKD stage 3B (eGFR range 30–45 mL/min/1.73 m²), CKD stage 4 (eGFR range 15–30 mL/min/1.73 m²), CKD stage 5 (eGFR <15 mL/min/1.73 m²). CI, confidence interval; CKD-CG, CKD-Cockcroft–Gault.

(NHANES) study 1988–1994 and the 1999–2004 NHANES study, the prevalence of CKD increased from 5.4% to 7.7% over this period.¹⁷ In clinical practice, an eGFR < 60 mL/minutes/1.73 m² serves as an indicator of CKD. However, using a different formula to calculate the eGFR may classify these patients differently. Using the CKD-CG formula, 38.3% of patients had CKD in this study, but only 21.7% when using the CKD-EPI formula. The coexistence of lung cancer and CKD is reported at approximately 13%.^{4,5} In this study, we observed a higher proportion of CKD patients, which could be related to the high incidence and prevalence of CKD in southern Taiwan (513/million and 3297/million, respectively).¹⁸

The overall prognosis for lung cancer is dismal, with a five-year relative survival rate of only 19.9%.¹⁹ In a small retrospective study of 107 patients, Patel *et al.* reported similar survival rates for CKD and non-CKD lung cancer patients using an eGFR of ≤ 90 mL/minute/1.73 m² to define CKD.⁶ We believe that the CKD patient sample used by Patel *et al.* with a mean eGFR of 71 mL/min/1.73 m² had a renal function that is too good to be considered CKD patients. In a previous retrospective report using the CG formula, Lu *et al.* found similar rates of survival between CKD and non-CKD patients.⁸ Xie *et al.* recommended using the CKD-EPI formula for Chinese patients to detect CKD based on the correlation, precision, limit of agreement, and simplicity compared to other formulas.²⁰ We used two formulas to evaluate the effect of different GFR estimations on lung cancer survival. Using the CKD-CG formula, the median survival of non-CKD patients was 10.61 months (95% CI 9.33–11.89) compared to 10.58 months (95% CI 9.03–12.13) in the CKD group ($P = 0.76$); while the median survival was 9.10 months (95% CI 8.01–10.20) for the non-CKD group compared to 7.59 months (95% CI 6.50–8.68) for the CKD group ($P = 0.19$) when using the CKD-EPI formula. We conclude that the survival rates in CKD and non-CKD patients did not differ significantly using either formula.

Lung cancer is most frequently diagnosed among people aged 65–74, with a median age at diagnosis of 70 years, according to the Surveillance, Epidemiology, and End Results Cancer Statistics Review, 1975–2015.¹⁹ In the present report, the median age at diagnosis was 71 using the CKD-CG formula and 75 using the CKD-EPI formula. We found that older patients had higher mortality rates, with a HR of 1.02 using the CKD-CG and CKD-EPI formulas (Table 5). Older patients were more inclined to choose no treatment/supportive treatment, more significantly deviating from treatment protocol because of intolerance to side effects, and a lack of suitability for radical surgical resection, which could result in the inferior survival rates compared to younger patients. Kale *et al.* reported four-fold to six-fold increases in toxicity related to chemoradiation

therapy in elderly patients with advanced stage lung cancers²¹ however, the survival rates of elderly patients (> 75 years) after radical treatment did not differ significantly from those of younger patients.²²

Several studies have reported gender differences in lung cancer survival.^{23–25} According to Wisnivesky *et al.*, women have better lung cancer-specific, overall, and relative survival than men in all treatment groups.²⁴ The gender-related differences in cancer affecting both sexes are more prominent in lung cancer at localized, regional, and unknown stages.²⁶ Sagerup *et al.* reported that regardless of stage, age, the period of diagnosis, and selected histological subgroups, men had an increased risk of death at five-years.²⁷ According to recent cancer statistics in the United States, the five-year relative survival by gender for all races was 21.5% for women and 15.4% for men.² Analysis of our data revealed different gender-difference outcomes using the CKD-CG and CKD-EPI formulas. Using the CKD-CG formula, men had an 11% higher risk of death (HR 1.11, 95% CI 0.96–1.28; $P = 0.18$) than women and the increased risk of death was 24% according to the CKD-EPI formula (HR 1.24, 1.07–1.43; $P = 0.01$) (Table 5). This difference in gender-related survival deserves further investigation.

Patients usually present at advanced stages of lung cancer at the time of diagnosis. In this report, survival rates by

cancer stage between CKD and non-CKD patients according to either formula did not differ significantly (Table 3). The survival rates by cancer stage (stage I–IIIA and IIIB–IV) for the different stages of renal impairment (non-CKD, CKD 3A, CKD 3B, CKD 4, and CKD 5) were different according to the formula used to estimate GRF. Using the CKD-CG formula, the survival differences were statistically significant for cancer stages I–IIIA and IIIB–IV. However, using the CKD-EPI formula, the survival differences were significant for cancer stage IIIB–IV ($P < 0.001$), but not for IA–IIIA ($P = 0.054$) (Table 4). Because the survival rate estimated for patients with cancer I–IIIA/CKD stage 4 via the CKD-EPI formula was significantly higher (median survival 42.35 vs. CKD-CG 14.88 months), this may have affected the statistical results. The survival rate did not differ significantly between CKD and non-CKD groups based on the type of treatment administered (medical or surgical) when using either formula. However, the survival rate for CKD patients was significantly lower when using CKD-EPI formula ($P = 0.04$) (Table 3).

While surgical resection is recommended for early-stage lung cancer and offers the best prospect of cure, physical fitness and medical comorbidities may prevent early-stage patients from undergoing surgical resection. The presence of comorbidities frequently influences the treatment selection for lung cancer patients. Iachina *et al.* evaluated the

Table 5 Adjusted Cox proportional hazard analysis for CKD group based on CKD-CG and CKD-EPI formulas

Characteristics	CKD-CG			CKD-EPI		
	Adjusted HR	95% CI	<i>P</i>	Adjusted HR	95% CI	<i>P</i>
Age	1.02	1.01–1.02	< 0.001	1.02	1.02–1.03	< 0.001
Gender						
Female	Ref			Ref		
Male	1.11	0.96–1.28	0.18	1.24	1.07–1.43	0.004
Comorbidity score	1.06	1.04–1.09	< 0.001	1.06	1.04–1.08	< 0.001
Smoking history						
No	Ref			Ref		
Yes	1.15	1.00–1.33	0.05	1.12	0.98–1.28	0.11
CKD status						
No	Ref			Ref		
Yes	0.96	0.88–1.08	0.65	1.05	0.95–1.17	0.33
Stage						
IA–IIIA	Ref			Ref		
IIIB–IV	1.73	1.45–2.07	< 0.001	1.81	1.52–2.16	< 0.001
Histology						
NSCLC	Ref			Ref		
SCLC	1.59	1.33–1.90	< 0.001	1.76	1.49–2.07	< 0.001
Treatment						
Supportive	1.96	1.71–2.25	< 0.001	2.00	1.77–2.25	< 0.001
Medical	Ref			Ref		
Surgical	0.37	0.29–0.47	< 0.001	0.45	0.35–0.57	< 0.001

Using the chronic kidney disease Cockcroft–Gault (CKD-CG) formula, lung cancer patients with CKD showed a 4% decrease in survival and a 5% increased risk of death using the CKD-Epidemiology Collaboration (CKD-EPI) formula. CKD is not an independent predictor for lung cancer survival regardless of the formula used to estimation the glomerular filtration rate. Younger patients, women, lower comorbidity scores, cancer stages I–IIIA, and surgical treatment were associated with improved survival. HR, hazard ratio; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

effect of different comorbidities on lung cancer survival.²⁸ They found that cardiovascular disease, diabetes, cerebrovascular disorders, and chronic obstructive pulmonary disease have a significant impact on survival in NSCLC patients. Unfortunately, because renal disease and other comorbidities were grouped together, the independent effect of CKD was not evaluated.²⁷ In this report, we summed each of the independent morbidity scores to a total score and graded them according to the median. Although OS rates in the CKD and non-CKD groups were not statistically significantly different using either formula, we found a consistently increased risk of mortality in Cox proportional hazard analysis (Table 5).

Results of the interface between lung cancer mortality outcome and the coexistence of CKD are conflicting. Na *et al.* reported that an eGFR of < 60 mL/minutes is associated with a 12% increase in the overall mortality rate for several types of cancer, but not lung cancer, independent of other known risk factors.⁴ Lu *et al.* found a 6% increased risk of death for CKD patients; however, this result was not statistically significant (HR 1.06, 95% CI 0.93–1.22; $P = 0.41$).⁸ In a recent population-based cohort study in Taiwan of lung cancer patients with coexisting CKD, Wei *et al.* found that CKD increased the mortality risk by 38%.⁷ The authors used specific International Classification of Disease codes to determine CKD and included mostly CKD stage 5 patients.⁷ In this study, the CKD-CG showed a 4% decrease in survival in lung cancer patients with CKD (HR 0.96, 95% 0.88–1.08; $P = 0.65$) while the CKD-EPI showed a 5% increased risk of death (HR 1.05, 95% CI 0.95–1.17; $P = 0.33$) (Table 5). CKD was not an independent predictor of lung cancer survival, regardless of the formula used to estimate GFR.

The retrospective design of this study, the absence of standardized and possible overlapping treatments, and the somewhat small number of patients may have influenced the survival outcomes reported and are the major limitations of this report. We caution extrapolation of the same conclusion in other populations because of the high incidence of CKD in our cohort.

In our limited experience of Taiwanese patients, CKD with an eGFR < 60 mL/minute/1.73 m² is not an independent risk factor for lung cancer survival. Lung cancer survival did not differ significantly between CKD and non-CKD patients either using the CKD-EPI or CKD-CG formulas. Patients with good physical performance should be administered radical treatment.

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Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Figure S1. Recruitment flow process.