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Treatment delay after non-small cell lung cancer diagnosis impacts patient survival rate: A National Cohort study

Running head: Treatment delay and survival for non-small cell lung cancer

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Abstract

OBJECTIVES. This study aimed to determine if treatment delay after non-small cell lung cancer (NSCLC) diagnosis impacts patient survival rate.

STUDY DESIGN. This study is a natural experiment in Taiwan. A retrospective cohort investigation was conducted from 2004 to 2010, which included 42,962 patients with newly diagnosed NSCLC.

METHODS. We identified 42,962 patients with newly diagnosed NSCLC in the Taiwan Cancer Registry from 2004 to 2010. We calculated the time interval between diagnosis and treatment initiation. All patients were followed from the index date to death, or the end of 2012. Cox proportional hazard models were used to examine the relationship between mortality and time interval.

RESULTS. We included 42,962 patients (15,799 men and 27,163 women) with newly diagnosed NSCLC. The mortality rate exhibited a significantly positive correlation to time interval from cancer diagnosis to treatment initiation. The adjusted hazard ratios ranged from 1.04 to 1.08 in all subgroups time interval more than 7 days compared with the counterpart subgroup of the interval from cancer diagnosis to treatment ≤7 days. The trend was also noted regardless of the patients with lung cancer in stage I, stage II, and stage III-IV.

CONCLUSIONS. Timeliness of treatment for NSCLC was crucial to improve the survival rate of patients with NSCLC, especially in stage I and II. We suggest patients with NSCLC should receive treatment as early as possible since the diagnosis was confirmed.

Strengths and limitations of this study

- We collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date.
- We investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III& IV) with pathological confirmation.
- The information on individual lifestyle, health behaviors, which may also affect the results, is not available.

Keywords: lung cancer; non-small cell lung cancer; delay treatment; timeliness of treatment; survival

INTRODUCTION

Lung cancer is among the most common causes of cancer death, particularly in industrialized countries.[1] In addition, the incidence of lung cancer has been gradually increasing over the last 50 years,[2] becoming a worldwide public health issue.[3] Lung cancer can be classified into small cell lung cancer and non-small cell lung cancer, of which the latter accounts for 80% of all lung cancer cases.[4] Despite recent improvements in treatment, the prognosis for lung cancer patients is still poor. Regardless of whether a patient has non-small cell lung cancer or small cell lung cancer, the 5-year survival rate is only 17.4%.[2 5-7] Most lung cancers are in the late stage (stages IIIB or IV) when diagnosed, which is likely to be a result of the long interval between the onset of symptoms and diagnosis.[8] There are often large differences in the length of the interval from the first appearance of symptoms to confirmation of diagnosis and treatment initiation in these patients.[4] Although there were many relevant studies on whether differences in the time delay between diagnosis to treatment initiation affects the prognosis of lung cancer patients, no definitive conclusion has been reached.[4] An increasing number of relevant studies have also highlighted the importance of this topic.

In Taiwan, 99.68% of the populace is covered by National Healthcare Insurance (NHI) program, which is a national insurance scheme that provides convenient

medical consultations and highly accessible treatment.[9] Under this system, lung cancer is classified as a catastrophic illness and is exempt from treatment-related fees, thereby that patients are not affected by economic factor. According to 2016 statistics from the Taiwan Ministry of Health and Welfare, cancer has consistently been the top cause of death. Among various types of cancer, lung cancer ranks first in the cause of death, with a mortality rate of 39.9 per 100,000 people. Therefore, it is important for public health providers to improve lung cancer prognoses and increase survival rates. This study aims to utilize national large-scale statistical data to investigate whether the interval between lung cancer diagnosis and treatment affects survival rate; concurrently, we also aim to examine the impact of other relevant factors on survival. This will provide a reference for future treatment for lung cancer patients of improving their survival.

METHODS

Data sources and participants

We included 55,014 newly diagnosed non-small cell lung cancer patients from 2004 to 2010. The newly diagnosed non-small cell lung cancer patients were defined as ICD-O-3 with C339 to C349 without any cancers before. Then we excluded those lung cancer patients with unknown stage for 3,993 patients. We also excluded lung cancer patients in situ (70 patients), with multiple cancer (1,298 patients), palliative

treatment in first year (1,934 patients), mortality before lung cancer diagnosed (64 patients), personal characteristics data missing (109 patients), and hospital data missing (4,584 patients). Finally, we had 42,962 people.

The data for this study was obtained from the Taiwan Cancer Registry, which was used to acquire study participants. We also linked this data to the National Health Insurance Database and the Cause of Death File from 2002 to 2012 that was provided by the Ministry of Health and Welfare.

Patient and public involvement

No patients were involved in this study, as it was based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan.

Variable descriptions

In this study, with regards to the variables used, the general characteristics of lung cancer patients included sex and age. Age was defined as the age at which the patient had a confirmatory diagnosis by pathology. The financial status of the patient was based on their monthly salary. The degree of urbanization at the patient's place of residence was used to represent environmental factors. The level of urbanization was based on 7 levels of classification from highly urbanized developed cities (level 1) to remote areas (level 7). The health status of the patient included data on whether the

patient had other catastrophic illnesses besides cancer, their Charlson Comorbidity Index (CCI), and the stage of non-small cell lung cancer. The definition of catastrophic illness was based on the 30 types of catastrophic illnesses or injuries as defined by the National Health Insurance Administration, which include stroke, chronic kidney failure, systemic lupus erythematosus, type I diabetes and severe mental illness. The degree of comorbidity was classified into three levels based on the CCI [10]. Tumor staging was based on the guidelines of the American Joint Committee on Cancer (6th edition for tumors diagnosed from 2004-2009, 7th edition for tumors diagnosed in 2010), which includes stages I, II, III, and IV. Hospital attributes include the level of hospital (medical centers, regional hospitals, district hospitals, and others), hospital ownership (public or private institutions), and the volume of hospital services (low, medium, high) in treatment of non-small cell lung cancer patients. The volume of hospital services was divided into low, medium, and high on the basis of quartiles: service volumes of <25%, 25-75% and >75% were defined as low, medium and high, respectively. Patients were considered to be enrolled in multidisciplinary team (MDT) care if they received MDT treatment after pathological diagnosis of non-small cell lung cancer; the definition of MDT is based on patients who were declared MDT treatment fees in the NHI database (47079B). The interval between diagnosis of non-small cell lung cancer and treatment initiation was defined as the

period between pathological sectioning and diagnosis of non-small cell lung cancer after biopsy to the time when the patient underwent their first treatment (including surgery, radiotherapy, or chemotherapy). The operating definition of relevant treatments is based on the relevant treatment code that was declared in the NHI database, which was checked against the treatment registration information in the Taiwan Cancer Information Database.

Main outcome measurements

The main outcome examined in this study was the survival rate of lung cancer patients. Confirmation of death was based on patient data from the NHI database and this was compared with the Taiwan Cause of Death archives for confirmation.

Statistical analysis

We employed descriptive statistics to show general characteristics (gender and age of cancer onset), financial status (monthly salary), environmental factors (level of urbanization of place of residence), health status of patients (catastrophic illnesses other than cancer, CCI, cancer stage), hospital attributes (level and ownership of hospital, annual service volume of the hospital), enrolment in MDT and the distribution status of the interval from diagnosis confirmation to treatment initiation in lung cancer patients who had a confirmatory diagnosis by pathology from 2004 to 2010. Following this, bivariate analysis was performed using the log-rank test to

investigate whether there were significant differences between survival status by the end of 2012 and the interval from diagnosis to treatment initiation. We then used univariate Cox proportional hazards regression to analyze relevant prognostic factors that affect the survival of lung cancer patients. The adjusted Cox proportional hazards model was used to investigate the relative risk of survival of lung cancer patients with different cancer stages with different intervals from diagnosis confirmation to treatment initiation, after controlling for related variables. Independent variables included patient characteristics, financial status, environmental factors, health status, hospital attributes, enrolment in MDT, and grouping of time to treatment initiation. The dependent variable was survival. Lastly, after controlling for relevant variables, the adjusted Cox proportional hazards model was used to generate survival curves for lung cancer patients of various stages and with different interval periods.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). A P value <0.05 was regarded as statistically significant and all tests were two-sided. This study was approved by the Institutional Review Board of Cheng Ching Hospital Chung Kang Branch (IRB number: HP150003).

RESULTS

Descriptive statistics of lung cancer patient characteristics for different treatment intervals

This study consisted of 46,962 non-small cell lung cancer patients. Out of all

non-small cell lung cancer patients, 36.70% patients had an initial treatment within seven days, while 12.54% patients received their initial treatments more than 61 days after cancer diagnosed. In all non-small cell lung cancer patients, the mean 5-year survival rate was 17.61%. As the interval from diagnosis to treatment initiation increased, the 5-year survival rate decreased from 26.12% to 6.02% (Table 1).

Table 1. Bivariate analysis of non-small cell lung cancer patient characteristics for different treatment intervals

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Total number	42,962	100.00	15,769	36.70	9,296	21.64	12,510	29.12	5,387	12.54	-
Five-year survival rate	42,962	17.61	15,769	26.12	9,296	15.96	12,510	12.99	5,387	6.02	<0.001
Gender											<0.001
Female	15,799	36.77	6,154	38.95	3,235	20.48	4,419	27.97	1,991	12.60	
Male	27,163	63.23	9,615	35.40	6,061	22.31	8,091	29.79	3,396	12.50	
Age											<0.001
≤ 44	2,106	4.90	889	42.21	455	21.60	568	26.97	194	9.21	
45~54	5,686	13.23	2,375	41.77	1,263	22.21	1,549	27.24	499	8.78	
55~64	9,155	21.31	3,634	39.69	2,033	22.21	2,658	29.03	830	9.07	
65~74	12,659	29.47	4,548	35.93	2,801	22.13	3,819	30.17	1,491	11.78	
≥ 75	13,356	31.09	4,323	32.37	2,744	20.55	3,916	29.32	2,373	17.77	
Mean age (m, sd)	66.76	12.44	65.52	12.55	66.45	12.22	67.04	12.15	70.25	12.46	<0.001
Monthly salary											<0.001

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Low-income	461	1.07	137	29.72	101	21.91	154	33.41	69	14.97	
≤ 17280	1,475	3.43	542	36.75	311	21.08	447	30.31	175	11.86	
17281~22800	22,935	53.38	8,074	35.20	5,079	22.15	6,751	29.44	3,031	13.22	
22801~28800	8,069	18.78	2,961	36.70	1,690	20.94	2,376	29.45	1,042	12.91	
28801~36300	2,676	6.23	1,011	37.78	588	21.97	782	29.22	295	11.02	
36301~45800	3,280	7.63	1,333	40.64	689	21.01	923	28.14	335	10.21	
≥ 45801	4,066	9.46	1,711	42.08	838	20.61	1,077	26.49	440	10.82	
Urbanization											0.186
Level 1	11,759	27.37	4,335	36.87	2,494	21.21	3,404	28.95	1,526	12.98	
Level 2	12,117	28.20	4,506	37.19	2,615	21.58	3,527	29.11	1,469	12.12	
Level 3	6,523	15.18	2,334	35.78	1,424	21.83	1,946	29.83	819	12.56	
Level 4	6,795	15.82	2,518	37.06	1,506	22.16	1,974	29.05	797	11.73	
Level 5	1,524	3.55	523	34.32	338	22.18	439	28.81	224	14.70	
Level 6	2,217	5.16	807	36.40	490	22.10	627	28.28	293	13.22	
Level 7	2,027	4.72	746	36.80	429	21.16	593	29.26	259	12.78	
CCI score											<0.001
≤ 3	20,388	47.46	7,475	36.66	4,576	22.44	6,186	30.34	2,151	10.55	
4~6	7,587	17.66	2,761	36.39	1,646	21.70	2,218	29.23	962	12.68	
≥ 7	14,987	34.88	5,533	36.92	3,074	20.51	4,106	27.40	2,274	15.17	
Other catastrophic illness											<0.001
No	41,474	96.54	15,300	36.89	8,984	21.66	12,076	29.12	5,114	12.33	

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Yes	1,488	3.46	469	31.52	312	20.97	434	29.17	273	18.35	
Cancer stage											<0.001
Stage I	5,681	13.22	3,226	56.79	910	16.02	1,269	22.34	276	4.86	
Stage II	1,526	3.55	589	38.60	338	22.15	462	30.28	137	8.98	
Stage III	11,696	27.22	4,030	34.46	2,843	24.31	3,500	29.92	1,323	11.31	
Stage IV	24,059	56.00	7,924	32.94	5,205	21.63	7,279	30.25	3,651	15.18	
MDT care											<0.001
No	37,716	87.79	13,669	36.24	8,012	21.24	10,974	29.10	5,061	13.42	
Yes	5,246	12.21	2,100	40.03	1,284	24.48	1,536	29.28	326	6.21	
Hospital level											<0.001
Medical centers	29,228	68.03	11,075	37.89	6,452	22.07	8,427	28.83	3,274	11.20	
Regional hospitals	12,601	29.33	4,395	34.88	2,655	21.07	3,787	30.05	1,764	14.00	
District hospitals	1,014	2.36	261	25.74	178	17.55	279	27.51	296	29.19	
Others	119	0.28	38	31.93	11	9.24	17	14.29	53	44.54	
Hospital ownership											<0.001
Public	16,770	39.03	6,619	39.47	3,776	22.52	4,558	27.18	1,817	10.83	
Private	26,192	60.97	9,150	34.93	5,520	21.08	7,952	30.36	3,570	13.63	
Hospital services volume											<0.001
Low	10,807	25.15	3,905	36.13	2,177	20.14	2,935	27.16	1,790	16.56	
Middle	21,043	48.98	7,519	35.73	4,652	22.11	6,486	30.82	2,386	11.34	
High	11,112	25.86	4,345	39.10	2,467	22.20	3,089	27.80	1,211	10.90	

[a] Log-rank test

Five-year survival rate of patients for different treatment intervals

At the same time, we found that in stage I patients, the 5-year survival rate decreased by 10.34% due to delayed treatment (patients with intervals >7 days). In stage II patients, if patients started treatment earlier (interval ≤7 days), their 5-year survival rate increased by 10.28%. Early treatment (interval ≤7 days) was found to have a smaller effect on 5-year survival rate in stage III and IV patients, with an increase in 5-year survival rate of 2.63% (Table 2).

Table 2. Five-year survival rate of patients for different treatment intervals

Variables	Stage I		Stage II		Stage III and IV		P value [a]
	N	%	N	%	N	%	
Total number	5,681	64.66	1,526	34.72	35,755	9.37	-
Interval from cancer diagnosis to treatment							<0.001
≤ 7 days	3,226	75	589	45	11,954	12	
8~14 days	910	62	338	34	8,048	10	
15~60 days	1,269	50	462	28	10,779	8	
≥ 61 days	276	20	137	15	4,974	5	

[a] Log-rank test

The effect of different treatment intervals on mortality risk in patients with lung cancer

Table 3 shows that when the group with interval from cancer diagnosis to treatment ≤7 days was used as a reference, the adjusted HR for mortality in other groups (8-14 days, 15-60 days, and ≥61 days) was significantly increased with increasing interval time (HR: 1.04-1.08). Among patients at various cancer stages, using stage I patients as a control group, the adjusted HRs for mortality for cancer patients at various stages was significantly higher (HR: 2.06-5.89) and the more advanced the cancer stages, the higher the adjusted HR for mortality. Patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

Table 3. Relative risk of death in patients for different treatment intervals

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value
Interval from cancer diagnosis to treatment						
≤ 7 days (ref.)						
8~14 days	**1.26**	<0.001	**1.04**	1.01	1.07	0.004
15~60 days	**1.30**	<0.001	**1.06**	1.04	1.09	<0.001
≥ 61 days	**1.66**	<0.001	**1.08**	1.04	1.11	<0.001

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value
Gender						
Female (ref.)						
Male	**1.54**	<0.001	**1.50**	1.47	1.53	<0.001
Age						
≤ 44 (ref.)						
45~54	**0.97**	0.357	**0.97**	0.92	1.03	0.351
55~64	**1.02**	0.478	**1.03**	0.97	1.09	0.331
65~74	**1.63**	<0.001	**1.27**	1.21	1.34	<0.001
≥ 75	**1.93**	<0.001	**1.79**	1.69	1.88	<0.001
Monthly salary						
Low-income (ref.)						
≤ 17280	**0.72**	<0.001	**0.89**	0.80	1.00	0.049
17281~22800	**0.81**	<0.001	**0.86**	0.78	0.95	0.002
22801~28800	**0.74**	<0.001	**0.83**	0.75	0.91	<0.001
28801~36300	**0.60**	<0.001	**0.79**	0.71	0.87	<0.001
36301~45800	**0.59**	<0.001	**0.78**	0.70	0.87	<0.001
≥ 45801	**0.56**	<0.001	**0.73**	0.66	0.81	<0.001
Urbanization level						
Level 1 (ref.)						
Level 2	**1.07**	<0.001	**0.99**	0.96	1.02	0.523
Level 3	**1.20**	<0.001	**1.04**	1.00	1.07	0.036
Level 4	**1.21**	<0.001	**1.01**	0.98	1.05	0.596
Level 5	**1.33**	<0.001	**1.01**	0.95	1.08	0.671

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value
Level 6	**1.39**	<0.001	**1.09**	1.04	1.15	0.001
Level 7	**1.25**	<0.001	**1.02**	0.96	1.07	0.570
CCI score						
≤ 3 (ref.)						
4~6	**1.35**	<0.001	**1.18**	1.14	1.21	<0.001
≥ 7	**1.80**	<0.001	**1.28**	1.25	1.31	<0.001
Other catastrophic illness						
No (ref.)						
Yes	**1.25**	<0.001	**1.26**	1.19	1.33	<0.001
Cancer stage						
Stage I (ref.)						
Stage II	**2.29**	<0.001	**2.06**	1.91	2.23	<0.001
Stage III	**4.48**	<0.001	**3.94**	3.75	4.13	<0.001
Stage IV	**6.51**	<0.001	**5.89**	5.62	6.17	<0.001
MDT care						
No (ref.)						
Yes	**0.95**	0.001	**0.91**	0.88	0.94	<0.001
Hospital level						
Medical centers (ref.)						
Regional hospitals	**1.28**	<0.001	**0.99**	0.96	1.02	0.347
District hospitals	**2.06**	<0.001	**1.25**	1.17	1.34	<0.001
Others	**1.17**	0.137	**0.90**	0.73	1.10	0.286
Hospital ownership						

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value
Public (ref.)						
Private	**1.27**	<0.001	**1.13**	1.10	1.16	<0.001
Hospital services volume						
Low (ref.)						
Middle	**0.72**	<0.001	**0.83**	0.81	0.85	<0.001
High	**0.59**	<0.001	**0.71**	0.68	0.74	<0.001

The effect of different treatment intervals on mortality risk in patients with lung cancer at different cancer stages

Table 4 shows that in stage I lung cancer patients, with patients with intervals of ≤7 days as the reference group, as the interval increased, the relative risk of death also significantly increased (HR: 1.45-2.41). This was also true for stage II (HR: 1.21-1.58) and the intervals between 15 days and 60 days of stage III and IV patients (HR: 1.03, 95% CI: 1.00-1.06). In stage III and IV patients, using patients with an interval ≤7 days as a reference group, the relative risk of death in patients with intervals ≥61 days was significantly increased (HR: 1.06, 95% CI: 1.02-1.09).

Table 4. Relative risk of death in patients for different treatment intervals and at different cancer stages

Variables	Stage I [a]			Stage II [a]			Stage III and IV [a]		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Interval from cancer diagnosis to treatment									
≤ 7 days (ref.)									
8~14 days	**1.45**	1.28	1.64	<0.001	**1.21**	1.01	1.45	0.039	**1.01**	0.98	1.04	0.526
15~60 days	**1.66**	1.49	1.84	<0.001	**1.44**	1.22	1.69	<0.001	**1.03**	1.00	1.06	0.045
≥ 61 days	**2.41**	2.06	2.83	<0.001	**1.58**	1.26	1.97	<0.001	**1.06**	1.02	1.09	0.002

a. Patient age, gender, monthly salary, level of urbanization of residence area, CCI score, other catastrophic illnesses, MDT care, hospital level, hospital ownership, and hospital services volume were controlled in all adjusted Cox proportional hazard models.

DISCUSSION

We found that the mortality rate exhibited significantly positive correlation to time interval from cancer diagnosis to treatment initiation in all stage NSCLC patients. The ratio of male to female in our study is similar to that in previous studies.[11 12] The delays between diagnosis and treatment can be categorized into three stages: namely, patient delay, diagnosis delay, and treatment delay.[2] Of all studies which investigated treatment delays in lung cancer patients, the study with the largest number of patients included 54,338 patients,[11] but was limited to non-metastatic lung cancer patients. In addition, the study only focused on patients who underwent surgical excision and did not analyze the treatment delay status and associated factors for all lung cancer patients. Another study collected data from 28,732 patients[13] to investigate whether treatment delay affects survival rate. The researchers found that if the interval from diagnosis to treatment was within 35 days, then there is improved survival for patients with localized disease, reduced survival for those with distant disease, but didn't have significant effect on patients with regional disease. However, in that study, the diagnosis to treatment interval was divided into just two groups (<35 days and >35 days), which makes it more difficult to show the correlation between different treatment delay groups and patient survival rates. In addition, in that study, the authors did not investigate whether different treatment delay periods affect

survival rate for different cancer stages as they only classified cancers as localized, regional, or distant. Another study included 20,561 patients[14]; however, this was only a descriptive statistical study and did not distinguish between the different cancer stages or examine relevant factors. The authors also did not carry out a correlation analysis between treatment delay and survival rate. To the best of our knowledge, the current study is the first large-scale nationwide study that examines whether treatment delay in non-small cell lung cancer affects patient survival rate. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate for different cancer stages (stages I, II, III and IV).

Previous studies have observed that if patients are older, have more comorbidities, or have stage I cancer, they are more likely to delay treatment (interval from diagnosis to treatment >30 days).[11] Similar findings were observed in our study: for patients aged ≥55 years, the greater the age the greater the proportion with treatment delay (interval ≥61 days) (Table 1). Patients with high CCI scores also demonstrated significantly increased proportions in treatment delay (interval ≥61 days) (Table 1). However, during analysis of the correlation between treatment delay and lung cancer stage, we found that the proportion of stage I patients with treatment delay was significantly lower than patients with other stages of lung cancer. A previous study has observed that in non-small cell lung cancer patients, treatment

delay is not associated with cancer stage.[15],[16-20] In contrast, treatment delay had more serious effects in stage III and IV patients.[21] However, in our study, we found that the proportion of stage I patients with treatment delay (interval from diagnosis to treatment ≥61 days) was significantly lower (4.86%, p<0.001), when compared with patients at other stages.

Previous studies have mentioned that in non-small cell lung cancer patients, our understanding of the effects of diagnosis and treatment delay on the prognosis of patients is limited, although an increasing number of recent studies are emphasizing the importance of this topic.[4] Some studies have found that in patients with a symptom-to-treatment interval (STI) of >60 days, the survival rate was significantly higher than that of patients with a STI of <60 days. However, if patients were further divided on the basis of the type of lung cancer, this difference was only significant in NSCLC patients. However, the number of patients included in this study was only 103 (96 men).[22] Two other studies, with 378 and 410 patients each, found that delaying diagnosis and treatment did not affect patient survival rates.[16] [17] Another study of 466 non-small cell lung cancer patients found that patients with shorter STIs had lower survival rates.[23] One study with 189 lung cancer patients found that treatment delay resulted in poorer prognosis for patients,[24] whilst another study with 132 patients found that longer specialist treatment delay does not result in poorer

prognosis.[25] An aforementioned article also observed that most previous studies in different countries were monocentric studies and that it is difficult to decide which study is most reliable with regards to whether treatment delay affects patient survival rates.[4]

Most studies show no relationship between time-to-chemotherapy (TTC) and their survival rate.[26] However, it should be noted that in these review articles, the number of cases collected is generally very low, with the highest number of patients only 10,583. In summary, the majority of previous studies into whether treatment delay affects survival rate in non-small cell lung cancer patients lack large-scale nationwide statistical data. This can easily lead to bias and produce divergent conclusions. In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and IV).

In addition, detailed examination of the literature found that a decreased treatment delay increases the risk of death in patients; the explanation provided for this is that a shorter treatment delay may mean that the patients have more obvious or more severe symptoms. Therefore, there is a need to correct the result with cancer stage and severity.[23] A previous study has also suggested that a shorter treatment

delay may reflect a requirement for more urgent treatment due to severity of symptoms, resulting in a poor prognosis.[27] Therefore, in this paper, we also considered the effects of cancer stage on treatment delay and patient prognosis. In another paper, it was also mentioned that the definition of treatment delay should be more standardized and accurate.[4] Another paper mentioned that it is not easy to accurately calculate the time of treatment initiation.[23] In addition, the calculation of patient delay (from symptom to doctor) is also prone to errors. Therefore, in this study, our definition of treatment delay was made according to the cancer registration archives and NHI database, from pathological diagnosis confirmation until treatment initiation.

For cancer patients in general, current medical guidelines all recommend early diagnosis and treatment to improve patient prognosis. However, early diagnosis is difficult due to multiple factors, such as non-apparent symptoms and patient delay. However, in this study, we found that if the interval from confirmation of pathological diagnosis to treatment initiation in non-small cell lung cancer patients is shortened to 7 days, this can effectively improve their 5-year survival rate (improvements of 2.63-10.34% were observed, according to the different stages of lung cancer). We also found that this improvement in 5-year survival rate was particularly marked for non-small cell lung cancer patients at early stages (stage I and II), at 10.28-10.34%.

However, in late stage (stage III and IV) patients, the 5-year survival rate was only increased by 2.63%. Therefore, we recommended that in future policies, treatment recommendations should be formulated so that patients can start treatment within 7 days after pathological diagnosis confirmation of non-small cell lung cancer to increase their 5-year survival rate. This is particularly important for early stage (stage I and II) non-small cell lung cancer patients, where improvement effects are more significant.

In this study, we also found that the effect of the interval from diagnosis to treatment initiation and patient survival rate decreased with more advanced cancer stages. Therefore, in patients who have stage I (HR: 1.45-2.41) or stage II (HR: 1.21-1.58) cancer, the longer the interval from diagnosis to treatment initiation, the higher the risk of death in patients. However, in stage III patients, compared with patients with an interval from diagnosis to treatment initiation ≤7 days, only when the interval from diagnosis to treatment initiation was >15 days was the risk of death increased. However, the magnitude of the increased risk of death is lower than in stage I and II patients (HR: 1.03-1.06). Therefore, this study found that timely treatment of stage I and II lung cancer patients has greater benefits. Therefore, we recommend that we should shorten the interval from diagnosis to treatment initiation especially in stage I and II lung cancer patients, thus decreasing the risk of death and

improving prognosis.

In recent studies, it was found that patients with oral cancers who underwent MDT treatment had significantly higher survival rates, and that the proportion of patients who underwent treatment was higher than those who did not joining MDT.[9] Previous studies have shown that the use of MDT care in cancer treatment can improve patient prognosis.[28] This is particularly the case in head and neck cancers, where MDT care is not only cost-effective but can also improve survival rates.[29] Previous studies have shown that in lung cancer patients MDT care can significantly improve the patient's acceptance of treatment, but does not significantly improve patient survival rates.[28] In this study, we found that patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

In summary, this study recommends that the interval from diagnosis to treatment initiation should be minimized during treatment of lung cancer patients at various cancer stages, particularly in stage I and II patients. In addition, in stage III and IV patients, we recommend the addition of MDT care to decrease the risk of death and improve prognosis.

Limitations

A secondary random database derived from the National Health Insurance

Research Database was employed for this study. The information on individual lifestyle, health behaviors, which may also affect the result, is not available.

Conclusions

In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III& IV) with pathological confirmation. Timeliness of treatment for NSCLC was crucial to improve the survival rate especially in stage I and II.

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Figure Legend

Figure 1. Adjusted survival curve in lung cancer patients with different cancer stages

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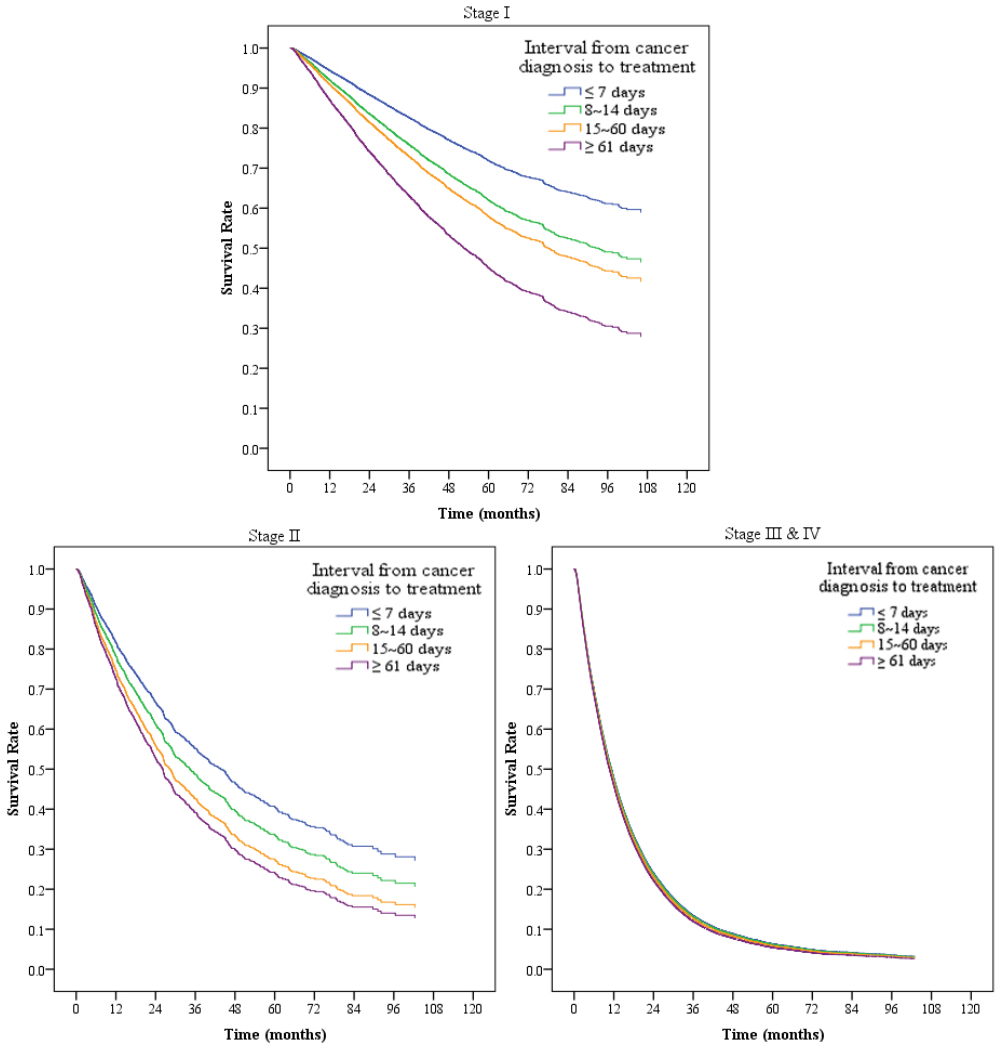

Figure 1

244x254mm (96 x 96 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			**5-6**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			**6-10**
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,9
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-19
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-19
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			20-26
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

Running head: Treatment delay and survival for non-small cell lung cancer

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Abstract

OBJECTIVES. This study aimed to determine if treatment delay after non-small cell lung cancer (NSCLC) diagnosis impacts patient survival rate.

STUDY DESIGN. This study is a natural experiment in Taiwan. A retrospective cohort investigation was conducted from 2004 to 2010, which included 42,962 patients with newly diagnosed NSCLC.

METHODS. We identified 42,962 patients with newly diagnosed NSCLC in the Taiwan Cancer Registry from 2004 to 2010. We calculated the time interval between diagnosis and treatment initiation. All patients were followed from the index date to death, or the end of 2012. Cox proportional hazard models were used to examine the relationship between mortality and time interval.

RESULTS. We included 42,962 patients (15,799 men and 27,163 women) with newly diagnosed NSCLC. The mortality rate exhibited significantly positive correlation to time interval from cancer diagnosis to treatment initiation. The adjusted hazard ratios ranged from 1.04 to 1.08 in all subgroups time interval more than 7 days compared with the counterpart subgroup of interval from cancer diagnosis to treatment ≤7 days. The trend was also noted regardless of the patients with lung cancer in stage I, stage II, and stage III.

CONCLUSIONS. Timeliness of treatment for NSCLC was crucial to improve the survival rate of patients with NSCLC especially in stages I and II. We suggest patients with NSCLC should receive treatment as early as possibility since the diagnosis was confirmed.

Strengths and limitations of this study

- It consisted of nationwide patients with non-small cell lung cancer.
- We collected nationwide data from 42,962 non-small cell lung cancer patients, which is the largest nationwide study to date.
- There were very few studies investigating treatment delay effects on the reduction of survival rate of lung cancer patients.
- Our lung cancer stages (stages I, II, III, and IV) were based on pathological confirmation.
- The information on individual lifestyle and health behaviors is not available.

Keywords: lung cancer; non-small cell lung cancer; delay treatment; timeliness of treatment; survival

INTRODUCTION

Lung cancer is among the most common causes of cancer death, particularly in industrialized countries.[1] In addition, the incidence of lung cancer has been gradually increasing over the last 50 years,[2] becoming a worldwide public health issue.[3] Lung cancer can be classified into small cell lung cancer and non-small cell lung cancer, of which the latter accounts for 80% of all lung cancer cases.[4] Despite recent improvements in treatment, the prognosis for lung cancer patients is still poor. Regardless of whether a patient has non-small cell lung cancer or small cell lung cancer, the 5-year survival rate is only 17.4%.[2 5-7] Most lung cancers are in the late stage (stages IIIB or IV) when diagnosed, which is likely to be a result of the long interval between the onset of symptoms and diagnosis.[8] There are often large differences in the length of the interval from the first appearance of symptoms to confirmation of diagnosis and treatment initiation in these patients.[4] Although there were many relevant studies on whether differences in the time delay between diagnosis to treatment initiation affects the prognosis of lung cancer patients, no definitive conclusion has been reached.[4] An increasing number of relevant studies have also highlighted the importance of this topic.

In Taiwan, 99.68% of the populace is covered by National Healthcare Insurance (NHI) program. Under this system, lung cancer is classified as a catastrophic illness and is exempt from treatment-related fees, thereby that patients are not affected by economic factor. According to 2016 statistics from the Taiwan Ministry of Health and Welfare, cancer has

consistently been the top cause of death. Among various types of cancer, lung cancer ranks first in the cause of death, with a mortality rate of 39.9 per 100,000 people. Therefore, it is important for public health providers to improve lung cancer prognoses and increase survival rates. The Taiwan Cancer Registry (TCR), a population-based cancer registry, was founded in 1979. The registry is organized by the Ministry of Health and Welfare. The Taiwan Cancer Registry Database (TCRD) records data of all types of cancer diagnosed and treatments in patients in Taiwan. The completeness (97%) and data quality of the Cancer Registry Database has achieved at an excellent level.[9] The accuracy of NHIRD has been validated in previous studies.[10] This study aims to utilize national large-scale statistical data to investigate whether the interval between lung cancer diagnosis and treatment affects survival rate; concurrently, we also aim to examine the impact of other relevant factors on survival. This will provide a reference for future treatment for lung cancer patients of improving their survival.

METHODS

Data sources and participants

We included 55,014 newly diagnosed non-small cell lung cancer patients from 2004 to 2010. The newly diagnosed non-small cell lung cancer patients were defined as ICD-O-3 with C339 to C349 without any cancers before. Then we excluded those lung cancer patients with unknown stage for 3,993 patients. We also excluded lung cancer patients in situ (70 patients), with multiple cancer (1,298 patients), palliative treatment at the beginning (1,934 patients),

mortality before lung cancer diagnosed (64 patients), personal characteristics data missing (109 patients), and hospital data missing (4,584 patients). In our study, patients with multiple cancers may affect survival due to other cancer effect. In Taiwan, palliative treatment is coded as special code in NHIRD. Non-small cell lung cancer patients with palliative treatment at beginning may be due to patients refusing further treatment or not receiving aggressive treatment. We excluded them for informal treatment. Otherwise, we also excluded those patients with data missing for accuracy. Finally, we had 42,962 people.

The data for this study was obtained from the Taiwan Cancer Registry, which was used to acquire study participants. We also linked this data to the National Health Insurance Database and the Cause of Death File from 2002 to 2012 that was provided by the Ministry of Health and Welfare. The accuracy of Taiwan Cancer Registry and NHIRD has achieved at an excellent level.

Patient and public involvement

No patients were involved in the planning, conception and design of this study, as this study was based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan.

Variable descriptions

In this study, with regards to the variables used, the general characteristics of lung cancer patients included sex and age. Age was defined as the age at which the patient had a

confirmatory diagnosis by pathology. The financial status of the patient was based on their monthly salary. The degree of urbanization at the patient's place of residence was used to represent environmental factors. The level of urbanization was based on 7 levels of classification from highly urbanized developed cities (level 1) to remote areas (level 7). The health status of the patient included data on whether the patient had other catastrophic illnesses besides cancer, their Charlson Comorbidity Index (CCI), and the stage of non-small cell lung cancer. The definition of catastrophic illness was based on the 30 types of catastrophic illnesses or injuries as defined by the National Health Insurance Administration, which include stroke, chronic kidney failure, systemic lupus erythematosus, type I diabetes and severe mental illness. The degree of comorbidity was classified into three levels based on the CCI [11]. Tumor staging was based on the guidelines of the American Joint Committee on Cancer (6th edition for tumors diagnosed from 2004-2009, 7th edition for tumors diagnosed in 2010), which includes stages I, II, III, and IV. Hospital attributes include the level of hospital (medical centers, regional hospitals, district hospitals, and others), hospital ownership (public or private institutions), and the volume of hospital services (low, medium, high) in treatment of non-small cell lung cancer patients. The volume of hospital services was divided into low, medium, and high on the basis of quartiles: service volumes of <25%, 25-75% and >75% were defined as low, medium and high, respectively. Patients were considered to be enrolled in multidisciplinary team (MDT) care if they received MDT treatment after pathological diagnosis of non-small cell lung cancer;

the definition of MDT is based on patients who were declared MDT treatment fees in the NHI database (47079B). The interval between diagnosis of non-small cell lung cancer and treatment initiation was defined as the period between pathological sectioning and diagnosis of non-small cell lung cancer after biopsy to the time when the patient underwent their first treatment (including surgery, radiotherapy, or chemotherapy). The operating definition of relevant treatments is based on the relevant treatment code that was declared in the NHI database, which was checked against the treatment registration information in the Taiwan Cancer Information Database.

Main outcome measurements

The main outcome examined in this study was the survival rate of lung cancer patients. Confirmation of death was based on patient data from the NHI database and this was compared with the Taiwan Cause of Death archives for confirmation.

Statistical analysis

We employed descriptive statistics to show general characteristics, financial status, environmental factors, health status of patients, hospital attributes, enrolment in MDT and the distribution status of the interval from diagnosis confirmation to treatment initiation in lung cancer patients who had a confirmatory diagnosis by pathology from 2004 to 2010. Following this, bivariate analysis was performed using the log-rank test to investigate whether there were significant differences between survival status by the end of 2012 and the interval from

diagnosis to treatment initiation. We then used univariate Cox proportional hazards regression to analyze relevant prognostic factors that affect the survival of lung cancer patients. The adjusted Cox proportional hazards model was used to investigate the relative risk of survival of lung cancer patients with different cancer stages with different intervals from diagnosis confirmation to treatment initiation, after controlling for related variables. Independent variables included patient characteristics, financial status, environmental factors, health status, hospital attributes, enrolment in MDT, and grouping of time to treatment initiation. The dependent variable was survival. Lastly, after controlling for relevant variables, the adjusted Cox proportional hazards model was used to generate survival curves for lung cancer patients of various stages and with different interval periods.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). A P value <0.05 was regarded as statistically significant and all tests were two-sided.

RESULTS

Descriptive statistics of lung cancer patient characteristics for different treatment intervals

In all lung cancer patients, the mean 5-year survival rate was 17.61%. As the interval from diagnosis to treatment initiation increased, the 5-year survival rate decreased from 26.12% to 6.02% (Table 1). We also included time to treatment with 0 day (TTT=0) cases in the <7 days group in our study. There were 7,363 cases with TTT=0 accounting for 17.14% of all patients

in our study. We had 3,258 females accounting for 44.25% in this subgroup. The age of diagnosed in most patients was from 65-74 years old accounting for 28.28% with mean age of 64.67 years old. The treatment of most patients with TTT=0 was surgery combining with radiotherapy and chemotherapy.

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Total number	42,962	100.00	15,769	36.70	9,296	21.64	12,510	29.12	5,387	12.54	-
Five-year survival rate	42,962	17.61	15,769	26.12	9,296	15.96	12,510	12.99	5,387	6.02	<0.001
Gender											<0.001
Female	15,799	36.77	6,154	38.95	3,235	20.48	4,419	27.97	1,991	12.60	
Male	27,163	63.23	9,615	35.40	6,061	22.31	8,091	29.79	3,396	12.50	
Age											<0.001
≤ 44	2,106	4.90	889	42.21	455	21.60	568	26.97	194	9.21	
45~54	5,686	13.23	2,375	41.77	1,263	22.21	1,549	27.24	499	8.78	
55~64	9,155	21.31	3,634	39.69	2,033	22.21	2,658	29.03	830	9.07	
65~74	12,659	29.47	4,548	35.93	2,801	22.13	3,819	30.17	1,491	11.78	
≥ 75	13,356	31.09	4,323	32.37	2,744	20.55	3,916	29.32	2,373	17.77	
Mean age (m, sd)	66.76	12.44	65.52	12.55	66.45	12.22	67.04	12.15	70.25	12.46	<0.001
Monthly salary											<0.001
Low-income	461	1.07	137	29.72	101	21.91	154	33.41	69	14.97	
≤ 17280	1,475	3.43	542	36.75	311	21.08	447	30.31	175	11.86	
17281~22800	22,935	53.38	8,074	35.20	5,079	22.15	6,751	29.44	3,031	13.22	
22801~28800	8,069	18.78	2,961	36.70	1,690	20.94	2,376	29.45	1,042	12.91	
28801~36300	2,676	6.23	1,011	37.78	588	21.97	782	29.22	295	11.02	
36301~45800	3,280	7.63	1,333	40.64	689	21.01	923	28.14	335	10.21	
≥ 45801	4,066	9.46	1,711	42.08	838	20.61	1,077	26.49	440	10.82	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Urbanization											0.186
Level 1	11,759	27.37	4,335	36.87	2,494	21.21	3,404	28.95	1,526	12.98	
Level 2	12,117	28.20	4,506	37.19	2,615	21.58	3,527	29.11	1,469	12.12	
Level 3	6,523	15.18	2,334	35.78	1,424	21.83	1,946	29.83	819	12.56	
Level 4	6,795	15.82	2,518	37.06	1,506	22.16	1,974	29.05	797	11.73	
Level 5	1,524	3.55	523	34.32	338	22.18	439	28.81	224	14.70	
Level 6	2,217	5.16	807	36.40	490	22.10	627	28.28	293	13.22	
Level 7	2,027	4.72	746	36.80	429	21.16	593	29.26	259	12.78	
CCI score											<0.001
≤ 3	20,388	47.46	7,475	36.66	4,576	22.44	6,186	30.34	2,151	10.55	
4~6	7,587	17.66	2,761	36.39	1,646	21.70	2,218	29.23	962	12.68	
≥ 7	14,987	34.88	5,533	36.92	3,074	20.51	4,106	27.40	2,274	15.17	
Other catastrophic illness											<0.001
No	41,474	96.54	15,300	36.89	8,984	21.66	12,076	29.12	5,114	12.33	
Yes	1,488	3.46	469	31.52	312	20.97	434	29.17	273	18.35	
Cancer stage											<0.001
Stage I	5,681	13.22	3,226	56.79	910	16.02	1,269	22.34	276	4.86	
Stage II	1,526	3.55	589	38.60	338	22.15	462	30.28	137	8.98	
Stage III	11,696	27.22	4,030	34.46	2,843	24.31	3,500	29.92	1,323	11.31	
Stage IV	24,059	56.00	7,924	32.94	5,205	21.63	7,279	30.25	3,651	15.18	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
MDT care											<0.001
No	37,716	87.79	13,669	36.24	8,012	21.24	10,974	29.10	5,061	13.42	
Yes	5,246	12.21	2,100	40.03	1,284	24.48	1,536	29.28	326	6.21	
Hospital level											<0.001
Medical centers	29,228	68.03	11,075	37.89	6,452	22.07	8,427	28.83	3,274	11.20	
Regional hospitals	12,601	29.33	4,395	34.88	2,655	21.07	3,787	30.05	1,764	14.00	
District hospitals	1,014	2.36	261	25.74	178	17.55	279	27.51	296	29.19	
Others	119	0.28	38	31.93	11	9.24	17	14.29	53	44.54	
Hospital ownership											<0.001
Public	16,770	39.03	6,619	39.47	3,776	22.52	4,558	27.18	1,817	10.83	
Private	26,192	60.97	9,150	34.93	5,520	21.08	7,952	30.36	3,570	13.63	
Hospital services volume											<0.001
Low	10,807	25.15	3,905	36.13	2,177	20.14	2,935	27.16	1,790	16.56	
Middle	21,043	48.98	7,519	35.73	4,652	22.11	6,486	30.82	2,386	11.34	
High	11,112	25.86	4,345	39.10	2,467	22.20	3,089	27.80	1,211	10.90	

[a] Log-rank test

Five-year survival rate of patients for different treatment intervals

At the same time, we found that in stage I patients, the 5-year survival rate decreased by 9.07% due to delayed treatment (patients with intervals >7 days). In stage

II patients, if patients started treatment earlier (interval ≤7 days), their 5-year survival rate increased by 9.01%. Early treatment (interval ≤7 days) was found to have a smaller effect on 5-year survival rate in stage III and stage IV patients, with an increase in 5-year survival rate of 1.91% and 0.49% (Table 2).

Table 2. Five-year survival rate of patients for different treatment intervals

Variables	Stage I		Stage II		Stage III		Stage IV		P value [a]
	N	%	N	%	N	%	N	%	
Total number	5,681	61.61	1,526	34.41	11,696	12.95	24,059	5.11	
Interval from cancer diagnosis to treatment									<0.001
≤ 7 days	3,226	70.68	589	43.42	4,030	14.86	7,924	5.60	
8~14 days	910	60.58	338	33.74	2,843	12.11	5,205	4.58	
15~60 days	1,269	49.07	462	29.81	3,500	13.81	7,279	5.43	
≥ 61 days	276	21.10	137	14.56	1,323	6.83	3,651	4.12	

[a] Log-rank test

The effect of different treatment intervals on mortality risk in patients with lung cancer

Table 3 shows that when the group with interval from cancer diagnosis to treatment ≤7 days was used as a reference, the adjusted HR for mortality in other groups (8-14 days, 15-60 days, and ≥61 days) was significantly increased with increasing interval time (HR: 1.04-1.08). Among patients at various cancer stages, using stage I patients as a control group, the adjusted HRs for mortality for cancer patients at various stages was significantly higher (HR: 2.06-5.89) and the more advanced the cancer stages, the higher the adjusted HR for mortality. Patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

Table 3. Relative risk of death in patients for different treatment intervals

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Interval from cancer diagnosis to treatment						
≤ 7 days (ref.)						
8~14 days	**1.26**	<0.001	**1.04**	1.01	1.07	0.004
15~60 days	**1.30**	<0.001	**1.06**	1.04	1.09	<0.001
≥ 61 days	**1.66**	<0.001	**1.08**	1.04	1.11	<0.001
Gender						
Female (ref.)						
Male	**1.54**	<0.001	**1.50**	1.47	1.53	<0.001
Age						
≤ 44 (ref.)						
45~54	**0.97**	0.357	**0.97**	0.92	1.03	0.351
55~64	**1.02**	0.478	**1.03**	0.97	1.09	0.331
65~74	**1.63**	<0.001	**1.27**	1.21	1.34	<0.001
≥ 75	**1.93**	<0.001	**1.79**	1.69	1.88	<0.001
Monthly salary						
Low-income (ref.)						
≤ 17280	**0.72**	<0.001	**0.89**	0.80	1.00	0.049
17281~22800	**0.81**	<0.001	**0.86**	0.78	0.95	0.002
22801~28800	**0.74**	<0.001	**0.83**	0.75	0.91	<0.001
28801~36300	**0.60**	<0.001	**0.79**	0.71	0.87	<0.001
36301~45800	**0.59**	<0.001	**0.78**	0.70	0.87	<0.001

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
≥ 45801	**0.56**	<0.001	**0.73**	0.66	0.81	<0.001
Urbanization level						
Level 1 (ref.)						
Level 2	**1.07**	<0.001	**0.99**	0.96	1.02	0.523
Level 3	**1.20**	<0.001	**1.04**	1.00	1.07	0.036
Level 4	**1.21**	<0.001	**1.01**	0.98	1.05	0.596
Level 5	**1.33**	<0.001	**1.01**	0.95	1.08	0.671
Level 6	**1.39**	<0.001	**1.09**	1.04	1.15	0.001
Level 7	**1.25**	<0.001	**1.02**	0.96	1.07	0.570
CCI score						
≤ 3 (ref.)						
4~6	**1.35**	<0.001	**1.18**	1.14	1.21	<0.001
≥ 7	**1.80**	<0.001	**1.28**	1.25	1.31	<0.001
Other catastrophic illness						
No (ref.)						
Yes	**1.25**	<0.001	**1.26**	1.19	1.33	<0.001
Cancer stage						
Stage I (ref.)						
Stage II	**2.29**	<0.001	**2.06**	1.91	2.23	<0.001
Stage III	**4.48**	<0.001	**3.94**	3.75	4.13	<0.001
Stage IV	**6.51**	<0.001	**5.89**	5.62	6.17	<0.001
MDT care						
No (ref.)						

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Yes	**0.95**	0.001	**0.91**	0.88	0.94	<0.001
Hospital level						
Medical centers (ref.)						
Regional hospitals	**1.28**	<0.001	**0.99**	0.96	1.02	0.347
District hospitals	**2.06**	<0.001	**1.25**	1.17	1.34	<0.001
Others	**1.17**	0.137	**0.90**	0.73	1.10	0.286
Hospital ownership						
Public (ref.)						
Private	**1.27**	<0.001	**1.13**	1.10	1.16	<0.001
Hospital services volume						
Low (ref.)						
Middle	**0.72**	<0.001	**0.83**	0.81	0.85	<0.001
High	**0.59**	<0.001	**0.71**	0.68	0.74	<0.001

[a] Cox proportional hazards regression

The effect of different treatment intervals on mortality risk in patients with lung cancer at different cancer stages

Table 4 shows that in stage I lung cancer patients, with patients with intervals of ≤7 days as the reference group, as the interval increased, the relative risk of death also significantly increased (HR: 1.45-2.41). This was also true for stage II (HR: 1.21-1.58) and the intervals more than 60 days of stage III lung cancer patients (HR: 1.13, 95% CI: 1.06-1.21). In stage IV patients, using patients with an interval ≤7 days as a

reference group, the relative risk of death was without significantly difference. Figure 1 shows adjusted survival curve in lung cancer patients with different cancer stages.

Table 4. Relative risk of death in patients for different treatment intervals and at different cancer stages

Variables	Stage I [a]			Stage II [a]			Stage III [a]			Stage IV [a]		
	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]
Interval from cancer diagnosis to treatment												
≤ 7 days (ref.)												
8~14 days	**1.45**	1.28 1.64	<0.001	**1.21**	1.01 1.45	0.039	**1.04**	0.98 1.09	0.177	**0.99**	0.95 1.03	0.561
15~60 days	**1.66**	1.49 1.84	<0.001	**1.44**	1.22 1.69	<0.001	**1.02**	0.97 1.07	0.560	**1.01**	0.98 1.04	0.572
≥ 61 days	**2.41**	2.06 2.83	<0.001	**1.58**	1.26 1.97	<0.001	**1.13**	1.06 1.21	<0.001	**0.98**	0.94 1.02	0.249

a. Patient age, gender, monthly salary, level of urbanization of place of residence, CCI score, other illness, MDT care, hospital level, hospital ownership, and hospital services volume were all controlled for using various models.

[b] adjusted Cox proportional hazards model

DISCUSSION

We found that the mortality rate exhibited significantly positive correlation to time interval from cancer diagnosis to treatment initiation in all stage NSCLC patients. The ratio of male to female in our study is similar to that in previous studies.[12 13] The delays between diagnosis and treatment can be categorized into three stages: namely, patient delay, diagnosis delay, and treatment delay.[2] Of all studies which investigated treatment delays in lung cancer patients, the study with the largest number of patients included 54,338 patients, but was limited to non-metastatic lung cancer patients.[12] In addition, the study only focused on patients who underwent surgical excision and did not analyze the treatment delay status and associated factors for all lung cancer patients. Another study collected data from 28,732 patients to investigate whether treatment delay affects survival rate.[14] The researchers found that if the interval from diagnosis to treatment was within 35 days, then there is improved survival for patients with localized disease, reduced survival for those with distant disease, but didn't have significant effect on patients with regional disease.[14] However, in that study, the diagnosis to treatment interval was divided into just two groups (<35 days and >35 days), which makes it more difficult to show the correlation between different treatment delay groups and patient survival rates. In addition, in that study, the authors did not investigate whether different treatment delay periods affect survival rate for different cancer stages as they only

classified cancers as localized, regional, or distant. To the best of our knowledge, the current study is the first large-scale nationwide study that examines whether treatment delay in non-small cell lung cancer affects patient survival rate. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate for different cancer stages (stages I, II, III and IV).

Previous studies have observed that if patients are older, have more comorbidities, or have stage I cancer, they are more likely to delay treatment (interval from diagnosis to treatment >30 days).[12] Similar findings were observed in our study: for patients aged ≥55 years, the greater the age the greater the proportion with treatment delay (interval ≥61 days) (Table 1). Patients with high CCI scores also demonstrated significantly increased proportions in treatment delay (interval ≥61 days) (Table 1). However, during analysis of the correlation between treatment delay and lung cancer stage, we found that the proportion of stage I patients with treatment delay was significantly lower than patients with other stages of lung cancer. A previous study has observed that in non-small cell lung cancer patients, treatment delay is not associated with cancer stage.[15,16-20] In contrast, treatment delay had more serious effects in stage III and IV patients.[21] However, in our study, we found that the proportion of stage I patients with treatment delay (interval from diagnosis to treatment ≥61 days) was significantly lower (4.86%, $p<0.001$), when compared with patients at other stages.

Previous studies have mentioned that in non-small cell lung cancer patients, our understanding of the effects of diagnosis and treatment delay on the prognosis of patients is limited, although an increasing number of recent studies are emphasizing the importance of this topic.[4] Some studies have found that in patients with a symptom-to-treatment interval (STI) of >60 days, the survival rate was significantly higher than that of patients with a STI of <60 days.[22] However, if patients were further divided on the basis of the type of lung cancer, this difference was only significant in NSCLC patients.[22] However, the number of patients included in this study was only 103 (96 men).[23] Two other studies, with 378 and 410 patients each, found that delaying diagnosis and treatment did not affect patient survival rates.[16 17] Another study of 466 non-small cell lung cancer patients found that patients with shorter STIs had lower survival rates.[24] One study with 189 lung cancer patients found that treatment delay resulted in poorer prognosis for patients,[25] whilst another study with 132 patients found that longer specialist treatment delay does not result in poorer prognosis.[26] An aforementioned article also observed that most previous studies in different countries were monocentric studies and that it is difficult to decide which study is most reliable with regards to whether treatment delay affects patient survival rates.[4]

Most studies show no relationship between time-to-chemotherapy (TTC) and their survival rate.[27] However, it should be noted that in these review articles, the number of

cases collected is generally very low, with the highest number of patients only 10,583.[27] Another study showed time intervals from diagnosis to treatment were not associated with survival outcomes in NSCLC.[28] In this previous study, they discussed NSCLC patients with different treatment such as surgery, radiotherapy, systemic therapy and palliative care which were not discussed in our study. They also suggested that delays to treatment might impact on other outcomes other than survival. However, there were only 1,729 patients in this previous study.[28] In summary, the majority of previous studies into whether treatment delay affects survival rate in non-small cell lung cancer patients lack large-scale nationwide statistical data. This can easily lead to bias and produce divergent conclusions. In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and IV).

In addition, detailed examination of the literature found that a decreased treatment delay increases the risk of death in patients; the explanation provided for this is that a shorter treatment delay may mean that the patients have more obvious or more severe symptoms.[24] Therefore, there is a need to correct the result with cancer stage and severity.[24] A previous study has also suggested that a shorter treatment delay may

reflect a requirement for more urgent treatment due to severity of symptoms, resulting in a poor prognosis.[29] Therefore, in this paper, we also considered the effects of cancer stage on treatment delay and patient prognosis. In another paper, it was also mentioned that the definition of treatment delay should be more standardized and accurate.[4] Another paper mentioned that it is not easy to accurately calculate the time of treatment initiation.[24] In addition, the calculation of patient delay (from symptom to doctor) is also prone to errors. Therefore, in this study, our definition of treatment delay was made according to the cancer registration archives and NHI database, from pathological diagnosis confirmation until treatment initiation.

For cancer patients in general, current medical guidelines all recommend early diagnosis and treatment to improve patient prognosis. However, early diagnosis is difficult due to multiple factors, such as non-apparent symptoms and patient delay. However, in this study, we found that if the interval from confirmation of pathological diagnosis to treatment initiation in non-small cell lung cancer patients is shortened to 7 days, this can effectively improve their 5-year survival rate (improvements of 0.49-9.07% were observed, according to the different stages of lung cancer). We also found that this improvement in 5-year survival rate was particularly marked for non-small cell lung cancer patients at early stages (stage I and II), at 10.28-10.34%. However, in late stage (stage III and stage IV) patients, the 5-year survival rate was only increased by

1.91% and 0.49%. A previous study showed that NSCLC growth rate appeared to be highly variable and related to histological subtype which was not discussed in our study.[30] Doubling times can be quite variable in different stages of NSCLC. Another study showed that rapid tumor progression was noted in patients with untreated, predominantly stage III NSCLC.[31] In our study, table 4 shows stage III non-small cell lung cancer patients with the interval from diagnosis to treatment initiation more than 60 days had significantly higher relative risk of death than patients with an interval ≤7 days (HR: 1.13, 95% CI: 1.06-1.21). This may be due to rapid tumor progression characteristics of stage III NSCLC. However, the delay treatment effect is not significant in stage IV NSCLC patients, which may be associated with poor outcome and low survival rate in late stage of NSCLC. Therefore, we recommended that in future policies, treatment recommendations should be formulated so that patients can start treatment within 7 days after pathological diagnosis confirmation of non-small cell lung cancer to increase their 5-year survival rate. This is particularly important for early stage (stage I and II) non-small cell lung cancer patients, where improvement effects are more significant.

In this study, we also found that the effect of the interval from diagnosis to treatment initiation and patient survival rate decreased with more advanced cancer stages. Therefore, in patients who have stage I (HR: 1.45-2.41) or stage II (HR: 1.21-

1.58) cancer, the longer the interval from diagnosis to treatment initiation, the higher the risk of death in patients. However, in stage III patients, compared with patients with an interval from diagnosis to treatment initiation ≤7 days, only when the interval from diagnosis to treatment initiation was ≥ 61 days was the risk of death increased. However, the magnitude of the increased risk of death is lower than in stage I and II patients (HR: 1.03-1.06). Therefore, this study found that timely treatment of stage I and II lung cancer patients has greater benefits. Therefore, we recommend that we should shorten the interval from diagnosis to treatment initiation especially in stage I and II lung cancer patients, thus decreasing the risk of death and improving prognosis. However, due to data limitation, we used crude survival instead of disease free survival.

In recent studies, it was found that patients with oral cancers who underwent MDT treatment had significantly higher survival rates, and that the proportion of patients who underwent treatment was higher than those who did not joining MDT.[32] Previous studies have shown that the use of MDT care in cancer treatment can improve patient prognosis.[33] This is particularly the case in head and neck cancers, where MDT care is not only cost-effective but can also improve survival rates.[34] Previous studies have shown that in lung cancer patients MDT care can significantly improve the patient's acceptance of treatment, but does not significantly improve patient survival rates.[33] In this study, we found that patients who underwent MDT care had a significantly lower

adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

In summary, this study recommends that the interval from diagnosis to treatment initiation should be minimized during treatment of lung cancer patients at various cancer stages, particularly in stage I and II patients. In addition, in stage III and stage IV patients, we recommend the addition of MDT care to decrease the risk of death and improve prognosis.

Limitations

A secondary random database derived from the National Health Insurance Research Database was employed for this study. The information on individual lifestyle, health behaviors, which may also affect the result, is not available. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is not available in our database, and disease free survival is also not available in our database.

Conclusions

In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and

survival rate in different cancer stages (stages I, II, III and stage IV) with pathological confirmation. NSCLC patients with timeliness treatment in stage I and II have better survival rate than others.

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Competing interests

The authors declare that they have no competing interests.

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Patient consent form

As this study used anonymized secondary data retrieved from the Taiwan's National Health Insurance Research Database, the requirement for informed consent was waived by the ethics committee.

Data sharing

This study used the National Health Insurance Research Database published by the Ministry of Health, Taiwan. Due to legal restrictions imposed by the Taiwan government related to the Personal Information Protection Act, the database cannot be made publicly available. All researchers can apply for using the databases for conducting their studies. Requests for data can be sent as a formal proposal to the

Science Center of the Ministry of Health and Welfare (http://www.mohw.gov.tw/EN/Ministry/Index.aspx). Any raw data are not allowed to be brought out from the Science Center. Only the analytic outputs in format of table or figure can be printed out. The restrictions prohibited the authors from making the minimal data set publicly available.

Figure Legend

Figure 1. Adjusted survival curve in lung cancer patients with different cancer stages

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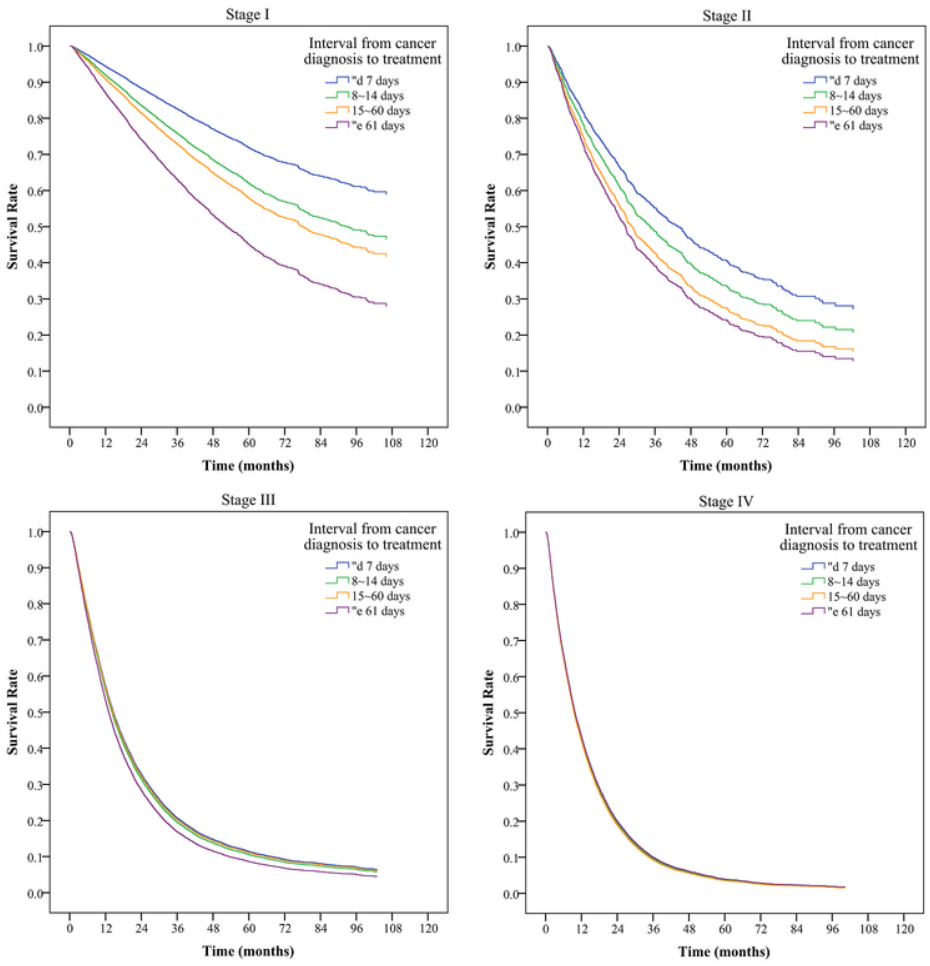

Figure 1

67x67mm (300 x 300 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			**5-6**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			**6-10**
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,9
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-19
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-19
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			20-26
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

Running head: Treatment delay and survival for non-small cell lung cancer

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Abstract

OBJECTIVES. This study aimed to determine if treatment delay after non-small cell lung cancer (NSCLC) diagnosis impacts patient survival rate.

STUDY DESIGN. This study is a natural experiment in Taiwan. A retrospective cohort investigation was conducted from 2004 to 2010, which included 42,962 patients with newly diagnosed NSCLC.

METHODS. We identified 42,962 patients with newly diagnosed NSCLC in the Taiwan Cancer Registry from 2004 to 2010. We calculated the time interval between diagnosis and treatment initiation. All patients were followed from the index date to death, or the end of 2012. Cox proportional hazard models were used to examine the relationship between mortality and time interval.

RESULTS. We included 42,962 patients (15,799 men and 27,163 women) with newly diagnosed NSCLC. The mortality rate exhibited a significantly positive correlation to time interval from cancer diagnosis to treatment initiation. The adjusted hazard ratios ranged from 1.04 to 1.08 in all subgroups time interval more than 7 days compared with the counterpart subgroup of the interval from cancer diagnosis to treatment ≤7 days. The trend was also noted regardless of the patients with lung cancer in stage I, stage II, and stage III.

CONCLUSIONS. There is a major association between time to treat and mortality of

patients with NSCLC, especially in stages I and II. We suggest patients with NSCLC should receive treatment as early as possible since the diagnosis was confirmed.

Strengths and limitations of this study

- It consisted of nationwide patients with non-small cell lung cancer.
- We collected nationwide data from 42,962 non-small cell lung cancer patients, which is the largest nationwide study to date.
- There were very few studies investigating treatment delay effects on the reduction of survival rate of lung cancer patients.
- Our lung cancer stages (stages I, II, III, and IV) were based on pathological confirmation.
- The information on individual lifestyle and health behaviors is not available.

Keywords: lung cancer; non-small cell lung cancer; delay treatment; timeliness of treatment; survival

INTRODUCTION

Lung cancer is among the most common causes of cancer death, particularly in industrialized countries.[1] In addition, the incidence of lung cancer has been gradually increasing over the last 50 years,[2] becoming a worldwide public health issue.[3] Lung cancer can be classified into small cell lung cancer and non-small cell lung cancer, of which the latter accounts for 80% of all lung cancer cases.[4] Despite recent improvements in treatment, the prognosis for lung cancer patients is still poor. Regardless of whether a patient has non-small cell lung cancer or small cell lung cancer, the 5-year survival rate is only 17.4%.[2 5-7] Most lung cancers are in the late stage (stages IIIB or IV) when diagnosed, which is likely to be a result of the long interval between the onset of symptoms and diagnosis.[8] There are often large differences in the length of the interval from the first appearance of symptoms to confirmation of diagnosis and treatment initiation in these patients.[4] Although there were many relevant studies on whether differences in the time delay between diagnosis to treatment initiation affects the prognosis of lung cancer patients, no definitive conclusion has been reached.[4] An increasing number of relevant studies have also highlighted the importance of this topic.

In Taiwan, 99.68% of the populace is covered by National Healthcare Insurance (NHI) program. Under this system, lung cancer is classified as a catastrophic illness and is exempt from treatment-related fees, thereby that patients are not affected by economic factor. According to 2016 statistics from the Taiwan Ministry of Health and Welfare, cancer has

consistently been the top cause of death. Among various types of cancer, lung cancer ranks first in the cause of death, with a mortality rate of 39.9 per 100,000 people. Therefore, it is important for public health providers to improve lung cancer prognoses and increase survival rates. The Taiwan Cancer Registry (TCR), a population-based cancer registry, was founded in 1979. The registry is organized by the Ministry of Health and Welfare. The Taiwan Cancer Registry Database (TCRD) records data of all types of cancer diagnosed and treatments in patients in Taiwan. The completeness (97%) and data quality of the Cancer Registry Database has achieved at an excellent level.[9] The accuracy of NHIRD has been validated in previous studies.[10] This study aims to utilize national large-scale statistical data to investigate whether the interval between lung cancer diagnosis and treatment affects survival rate; concurrently, we also aim to examine the impact of other relevant factors on survival. This will provide a reference for future treatment for lung cancer patients of improving their survival.

METHODS

Data sources and participants

We included 55,014 newly diagnosed non-small cell lung cancer patients from 2004 to 2010. The newly diagnosed non-small cell lung cancer patients were defined as ICD-O-3 with C339 to C349 without any cancers before. Then we excluded those lung cancer patients with unknown stage for 3,993 patients. We also excluded lung cancer patients in situ (70 patients), with multiple cancer (1,298 patients), palliative treatment at the beginning (1,934 patients),

mortality before lung cancer diagnosed (64 patients), personal characteristics data missing (109 patients), and hospital data missing (4,584 patients). In our study, patients with multiple cancers may affect survival due to other cancer effect. In Taiwan, palliative treatment is coded as special code in NHIRD. Non-small cell lung cancer patients with palliative treatment at beginning may be due to patients refusing further treatment or not receiving aggressive treatment. We excluded them for informal treatment. Otherwise, we also excluded those patients with data missing for accuracy. Finally, we had 42,962 people.

The data for this study was obtained from the Taiwan Cancer Registry, which was used to acquire study participants. We also linked this data to the National Health Insurance Database and the Cause of Death File from 2002 to 2012 that was provided by the Ministry of Health and Welfare. The accuracy of Taiwan Cancer Registry and NHIRD has achieved at an excellent level.

Patient and public involvement

No patients were involved in the planning, conception and design of this study, as this study was based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan.

Variable descriptions

In this study, with regards to the variables used, the general characteristics of lung cancer patients included sex and age. Age was defined as the age at which the patient had a

confirmatory diagnosis by pathology. The financial status of the patient was based on their monthly salary. The degree of urbanization at the patient's place of residence was used to represent environmental factors. The level of urbanization was based on 7 levels of classification from highly urbanized developed cities (level 1) to remote areas (level 7). The health status of the patient included data on whether the patient had other catastrophic illnesses besides cancer, their Charlson Comorbidity Index (CCI), and the stage of non-small cell lung cancer. The definition of catastrophic illness was based on the 30 types of catastrophic illnesses or injuries as defined by the National Health Insurance Administration, which include stroke, chronic kidney failure, systemic lupus erythematosus, type I diabetes and severe mental illness. The degree of comorbidity was classified into three levels based on the CCI [11]. Tumor staging was based on the guidelines of the American Joint Committee on Cancer (6th edition for tumors diagnosed from 2004-2009, 7th edition for tumors diagnosed in 2010), which includes stages I, II, III, and IV. Hospital attributes include the level of hospital (medical centers, regional hospitals, district hospitals, and others), hospital ownership (public or private institutions), and the volume of hospital services (low, medium, high) in treatment of non-small cell lung cancer patients. The volume of hospital services was divided into low, medium, and high on the basis of quartiles: service volumes of <25%, 25-75% and >75% were defined as low, medium and high, respectively. Patients were considered to be enrolled in multidisciplinary team (MDT) care if they received MDT treatment after pathological diagnosis of non-small cell lung cancer;

the definition of MDT is based on patients who were declared MDT treatment fees in the NHI database (47079B). The interval between diagnosis of non-small cell lung cancer and treatment initiation was defined as the period between pathological sectioning and diagnosis of non-small cell lung cancer after biopsy to the time when the patient underwent their first treatment (including surgery, radiotherapy, or chemotherapy). The operating definition of relevant treatments is based on the relevant treatment code that was declared in the NHI database, which was checked against the treatment registration information in the Taiwan Cancer Information Database.

Main outcome measurements

The main outcome examined in this study was the survival rate of lung cancer patients. Confirmation of death was based on patient data from the NHI database and this was compared with the Taiwan Cause of Death archives for confirmation.

Statistical analysis

We employed descriptive statistics to show general characteristics, financial status, environmental factors, health status of patients, hospital attributes, enrolment in MDT and the distribution status of the interval from diagnosis confirmation to treatment initiation in lung cancer patients who had a confirmatory diagnosis by pathology from 2004 to 2010. Following this, bivariate analysis was performed using the log-rank test to investigate whether there were significant differences between survival status by the end of 2012 and the interval from

diagnosis to treatment initiation. We then used univariate Cox proportional hazards regression to analyze relevant prognostic factors that affect the survival of lung cancer patients. The adjusted Cox proportional hazards model was used to investigate the relative risk of survival of lung cancer patients with different cancer stages with different intervals from diagnosis confirmation to treatment initiation, after controlling for related variables. Independent variables included patient characteristics, financial status, environmental factors, health status, hospital attributes, enrolment in MDT, and grouping of time to treatment initiation. The dependent variable was survival. Lastly, after controlling for relevant variables, the adjusted Cox proportional hazards model was used to generate survival curves for lung cancer patients of various stages and with different interval periods.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). A P value <0.05 was regarded as statistically significant and all tests were two-sided.

RESULTS

Descriptive statistics of lung cancer patient characteristics for different treatment intervals

In all lung cancer patients, the mean 5-year survival rate was 17.61%. As the interval from diagnosis to treatment initiation increased, the 5-year survival rate decreased from 26.12% to 6.02% (Table 1). We also included time to treatment with 0 day (TTT=0) cases in the <7 days group in our study. There were 7,363 cases with TTT=0 accounting for 17.14% of all patients

in our study. We had 3,258 females accounting for 44.25% in this subgroup. The age of diagnosed in most patients was from 65-74 years old accounting for 28.28% with mean age of 64.67 years old. The treatment of most patients with TTT=0 was surgery combining with radiotherapy and chemotherapy. The 5-year survival rate was 34.9% in this group with TTT=0.

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Total number	42,962	100.00	15,769	36.70	9,296	21.64	12,510	29.12	5,387	12.54	-
Five-year survival rate	42,962	17.61	15,769	26.12	9,296	15.96	12,510	12.99	5,387	6.02	<0.001
Gender											<0.001
Female	15,799	36.77	6,154	38.95	3,235	20.48	4,419	27.97	1,991	12.60	
Male	27,163	63.23	9,615	35.40	6,061	22.31	8,091	29.79	3,396	12.50	
Age											<0.001
≤ 44	2,106	4.90	889	42.21	455	21.60	568	26.97	194	9.21	
45~54	5,686	13.23	2,375	41.77	1,263	22.21	1,549	27.24	499	8.78	
55~64	9,155	21.31	3,634	39.69	2,033	22.21	2,658	29.03	830	9.07	
65~74	12,659	29.47	4,548	35.93	2,801	22.13	3,819	30.17	1,491	11.78	
≥ 75	13,356	31.09	4,323	32.37	2,744	20.55	3,916	29.32	2,373	17.77	
Mean age (m, sd)	66.76	12.44	65.52	12.55	66.45	12.22	67.04	12.15	70.25	12.46	<0.001
Monthly salary											<0.001
Low-income	461	1.07	137	29.72	101	21.91	154	33.41	69	14.97	
≤ 17280	1,475	3.43	542	36.75	311	21.08	447	30.31	175	11.86	
17281~22800	22,935	53.38	8,074	35.20	5,079	22.15	6,751	29.44	3,031	13.22	
22801~28800	8,069	18.78	2,961	36.70	1,690	20.94	2,376	29.45	1,042	12.91	
28801~36300	2,676	6.23	1,011	37.78	588	21.97	782	29.22	295	11.02	
36301~45800	3,280	7.63	1,333	40.64	689	21.01	923	28.14	335	10.21	
≥ 45801	4,066	9.46	1,711	42.08	838	20.61	1,077	26.49	440	10.82	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Urbanization											0.186
Level 1	11,759	27.37	4,335	36.87	2,494	21.21	3,404	28.95	1,526	12.98	
Level 2	12,117	28.20	4,506	37.19	2,615	21.58	3,527	29.11	1,469	12.12	
Level 3	6,523	15.18	2,334	35.78	1,424	21.83	1,946	29.83	819	12.56	
Level 4	6,795	15.82	2,518	37.06	1,506	22.16	1,974	29.05	797	11.73	
Level 5	1,524	3.55	523	34.32	338	22.18	439	28.81	224	14.70	
Level 6	2,217	5.16	807	36.40	490	22.10	627	28.28	293	13.22	
Level 7	2,027	4.72	746	36.80	429	21.16	593	29.26	259	12.78	
CCI score											<0.001
≤ 3	20,388	47.46	7,475	36.66	4,576	22.44	6,186	30.34	2,151	10.55	
4~6	7,587	17.66	2,761	36.39	1,646	21.70	2,218	29.23	962	12.68	
≥ 7	14,987	34.88	5,533	36.92	3,074	20.51	4,106	27.40	2,274	15.17	
Other catastrophic illness											<0.001
No	41,474	96.54	15,300	36.89	8,984	21.66	12,076	29.12	5,114	12.33	
Yes	1,488	3.46	469	31.52	312	20.97	434	29.17	273	18.35	
Cancer stage											<0.001
Stage I	5,681	13.22	3,226	56.79	910	16.02	1,269	22.34	276	4.86	
Stage II	1,526	3.55	589	38.60	338	22.15	462	30.28	137	8.98	
Stage III	11,696	27.22	4,030	34.46	2,843	24.31	3,500	29.92	1,323	11.31	
Stage IV	24,059	56.00	7,924	32.94	5,205	21.63	7,279	30.25	3,651	15.18	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
MDT care											<0.001
No	37,716	87.79	13,669	36.24	8,012	21.24	10,974	29.10	5,061	13.42	
Yes	5,246	12.21	2,100	40.03	1,284	24.48	1,536	29.28	326	6.21	
Hospital level											<0.001
Medical centers	29,228	68.03	11,075	37.89	6,452	22.07	8,427	28.83	3,274	11.20	
Regional hospitals	12,601	29.33	4,395	34.88	2,655	21.07	3,787	30.05	1,764	14.00	
District hospitals	1,014	2.36	261	25.74	178	17.55	279	27.51	296	29.19	
Others	119	0.28	38	31.93	11	9.24	17	14.29	53	44.54	
Hospital ownership											<0.001
Public	16,770	39.03	6,619	39.47	3,776	22.52	4,558	27.18	1,817	10.83	
Private	26,192	60.97	9,150	34.93	5,520	21.08	7,952	30.36	3,570	13.63	
Hospital services volume											<0.001
Low	10,807	25.15	3,905	36.13	2,177	20.14	2,935	27.16	1,790	16.56	
Middle	21,043	48.98	7,519	35.73	4,652	22.11	6,486	30.82	2,386	11.34	
High	11,112	25.86	4,345	39.10	2,467	22.20	3,089	27.80	1,211	10.90	

[a] Log-rank test

Five-year survival rate of patients for different treatment intervals

At the same time, we found that in stage I patients, the 5-year survival rate decreased by 9.07% due to delayed treatment (patients with intervals >7 days). In stage

II patients, if patients started treatment earlier (interval ≤7 days), their 5-year survival rate increased by 9.01%. Early treatment (interval ≤7 days) was found to have a smaller effect on 5-year survival rate in stage III and stage IV patients, with an increase in 5-year survival rate of 1.91% and 0.49% (Table 2).

Table 2. Five-year survival rate of patients for different treatment intervals

Variables	Stage I		Stage II		Stage III		Stage IV		P value [a]
	N	%	N	%	N	%	N	%	
Total number	5,681	61.61	1,526	34.41	11,696	12.95	24,059	5.11	
Interval from cancer diagnosis to treatment									<0.001
≤ 7 days	3,226	70.68	589	43.42	4,030	14.86	7,924	5.60	
8~14 days	910	60.58	338	33.74	2,843	12.11	5,205	4.58	
15~60 days	1,269	49.07	462	29.81	3,500	13.81	7,279	5.43	
≥ 61 days	276	21.10	137	14.56	1,323	6.83	3,651	4.12	

[a] Log-rank test

The effect of different treatment intervals on mortality risk in patients with lung cancer

Table 3 shows that when the group with interval from cancer diagnosis to treatment ≤7 days was used as a reference, the adjusted HR for mortality in other groups (8-14 days, 15-60 days, and ≥61 days) was significantly increased with increasing interval time (HR: 1.04-1.08). Among patients at various cancer stages, using stage I patients as a control group, the adjusted HRs for mortality for cancer patients at various stages was significantly higher (HR: 2.06-5.89) and the more advanced the cancer stages, the higher the adjusted HR for mortality. Patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

Table 3. Relative risk of death in patients for different treatment intervals

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Interval from cancer diagnosis to treatment						
≤ 7 days (ref.)						
8~14 days	**1.26**	<0.001	**1.04**	1.01	1.07	0.004
15~60 days	**1.30**	<0.001	**1.06**	1.04	1.09	<0.001
≥ 61 days	**1.66**	<0.001	**1.08**	1.04	1.11	<0.001
Gender						
Female (ref.)						
Male	**1.54**	<0.001	**1.50**	1.47	1.53	<0.001
Age						
≤ 44 (ref.)						
45~54	**0.97**	0.357	**0.97**	0.92	1.03	0.351
55~64	**1.02**	0.478	**1.03**	0.97	1.09	0.331
65~74	**1.63**	<0.001	**1.27**	1.21	1.34	<0.001
≥ 75	**1.93**	<0.001	**1.79**	1.69	1.88	<0.001
Monthly salary						
Low-income (ref.)						
≤ 17280	**0.72**	<0.001	**0.89**	0.80	1.00	0.049
17281~22800	**0.81**	<0.001	**0.86**	0.78	0.95	0.002
22801~28800	**0.74**	<0.001	**0.83**	0.75	0.91	<0.001
28801~36300	**0.60**	<0.001	**0.79**	0.71	0.87	<0.001
36301~45800	**0.59**	<0.001	**0.78**	0.70	0.87	<0.001

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
≥ 45801	**0.56**	<0.001	**0.73**	0.66	0.81	<0.001
Urbanization level						
Level 1 (ref.)						
Level 2	**1.07**	<0.001	**0.99**	0.96	1.02	0.523
Level 3	**1.20**	<0.001	**1.04**	1.00	1.07	0.036
Level 4	**1.21**	<0.001	**1.01**	0.98	1.05	0.596
Level 5	**1.33**	<0.001	**1.01**	0.95	1.08	0.671
Level 6	**1.39**	<0.001	**1.09**	1.04	1.15	0.001
Level 7	**1.25**	<0.001	**1.02**	0.96	1.07	0.570
CCI score						
≤ 3 (ref.)						
4~6	**1.35**	<0.001	**1.18**	1.14	1.21	<0.001
≥ 7	**1.80**	<0.001	**1.28**	1.25	1.31	<0.001
Other catastrophic illness						
No (ref.)						
Yes	**1.25**	<0.001	**1.26**	1.19	1.33	<0.001
Cancer stage						
Stage I (ref.)						
Stage II	**2.29**	<0.001	**2.06**	1.91	2.23	<0.001
Stage III	**4.48**	<0.001	**3.94**	3.75	4.13	<0.001
Stage IV	**6.51**	<0.001	**5.89**	5.62	6.17	<0.001
MDT care						
No (ref.)						

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Yes	**0.95**	0.001	**0.91**	0.88	0.94	<0.001
Hospital level						
Medical centers (ref.)						
Regional hospitals	**1.28**	<0.001	**0.99**	0.96	1.02	0.347
District hospitals	**2.06**	<0.001	**1.25**	1.17	1.34	<0.001
Others	**1.17**	0.137	**0.90**	0.73	1.10	0.286
Hospital ownership						
Public (ref.)						
Private	**1.27**	<0.001	**1.13**	1.10	1.16	<0.001
Hospital services volume						
Low (ref.)						
Middle	**0.72**	<0.001	**0.83**	0.81	0.85	<0.001
High	**0.59**	<0.001	**0.71**	0.68	0.74	<0.001

[a] Cox proportional hazards regression

The effect of different treatment intervals on mortality risk in patients with lung cancer at different cancer stages

Table 4 shows that in stage I lung cancer patients, with patients with intervals of ≤7 days as the reference group, as the interval increased, the relative risk of death also significantly increased (HR: 1.45-2.41). This was also true for stage II (HR: 1.21-1.58) and the intervals more than 60 days of stage III lung cancer patients (HR: 1.13, 95% CI: 1.06-1.21). In stage IV patients, using patients with an interval ≤7 days as a

reference group, the relative risk of death was without significantly difference. Figure 1 shows adjusted survival curve in lung cancer patients with different cancer stages.

Table 4. Relative risk of death in patients for different treatment intervals and at different cancer stages

Variables	Stage I [a]			Stage II [a]			Stage III [a]			Stage IV [a]		
	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]
Interval from cancer diagnosis to treatment												
≤ 7 days (ref.)												
8~14 days	**1.45**	1.28 1.64	<0.001	**1.21**	1.01 1.45	0.039	**1.04**	0.98 1.09	0.177	**0.99**	0.95 1.03	0.561
15~60 days	**1.66**	1.49 1.84	<0.001	**1.44**	1.22 1.69	<0.001	**1.02**	0.97 1.07	0.560	**1.01**	0.98 1.04	0.572
≥ 61 days	**2.41**	2.06 2.83	<0.001	**1.58**	1.26 1.97	<0.001	**1.13**	1.06 1.21	<0.001	**0.98**	0.94 1.02	0.249

a. Patient age, gender, monthly salary, level of urbanization of place of residence, CCI score, other illness, MDT care, hospital level, hospital ownership, and hospital services volume were all controlled for using various models.

[b] adjusted Cox proportional hazards model

DISCUSSION

We found that the mortality rate exhibited significantly positive correlation to time interval from cancer diagnosis to treatment initiation in all stage NSCLC patients. The ratio of male to female in our study is similar to that in previous studies.[12 13] The delays between diagnosis and treatment can be categorized into three stages: namely, patient delay, diagnosis delay, and treatment delay.[2] Of all studies which investigated treatment delays in lung cancer patients, the study with the largest number of patients included 54,338 patients, but was limited to non-metastatic lung cancer patients.[12] In addition, the study only focused on patients who underwent surgical excision and did not analyze the treatment delay status and associated factors for all lung cancer patients. Another study collected data from 28,732 patients to investigate whether treatment delay affects survival rate.[14] The researchers found that if the interval from diagnosis to treatment was within 35 days, then there is improved survival for patients with localized disease, reduced survival for those with distant disease, but didn't have significant effect on patients with regional disease.[14] However, in that study, the diagnosis to treatment interval was divided into just two groups (<35 days and >35 days), which makes it more difficult to show the correlation between different treatment delay groups and patient survival rates. In addition, in that study, the authors did not investigate whether different treatment delay periods affect survival rate for different cancer stages as they only

classified cancers as localized, regional, or distant. To the best of our knowledge, the current study is the first large-scale nationwide study that examines whether treatment delay in non-small cell lung cancer affects patient survival rate. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate for different cancer stages (stages I, II, III and IV).

Previous studies have observed that if patients are older, have more comorbidities, or have stage I cancer, they are more likely to delay treatment (interval from diagnosis to treatment >30 days).[12] Similar findings were observed in our study: for patients aged ≥55 years, the greater the age the greater the proportion with treatment delay (interval ≥61 days) (Table 1). Patients with high CCI scores also demonstrated significantly increased proportions in treatment delay (interval ≥61 days) (Table 1). CCI is a general score to evaluate patients' comorbidity and does not focus on lung cancer patients. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is more accurate for evaluating their severity but is not available in our study. It is a fact that patients with poorer lung function require additional testing to determine candidacy for surgery. This testing, including six minute walk test, quantitative perfusion scans, cardiopulmonary exercise testing and consultation with pulmonary medicine takes time and is not available in our study. However, during analysis of the correlation between treatment

delay and lung cancer stage, we found that the proportion of stage I patients with treatment delay was significantly lower than patients with other stages of lung cancer. A previous study has observed that in non-small cell lung cancer patients, treatment delay is not associated with cancer stage.[15],[16-20] In contrast, treatment delay had more serious effects in stage III and IV patients.[21] However, in our study, we found that the proportion of stage I patients with treatment delay (interval from diagnosis to treatment ≥61 days) was significantly lower (4.86%, $p<0.001$), when compared with patients at other stages.

Previous studies have mentioned that in non-small cell lung cancer patients, our understanding of the effects of diagnosis and treatment delay on the prognosis of patients is limited, although an increasing number of recent studies are emphasizing the importance of this topic.[4] Some studies have found that in patients with a symptom-to-treatment interval (STI) of >60 days, the survival rate was significantly higher than that of patients with a STI of <60 days.[22] However, if patients were further divided on the basis of the type of lung cancer, this difference was only significant in NSCLC patients.[22] However, the number of patients included in this study was only 103 (96 men).[23] Two other studies, with 378 and 410 patients each, found that delaying diagnosis and treatment did not affect patient survival rates.[16] [17] Another study of 466 non-small cell lung cancer patients found that patients with shorter STIs had lower

survival rates.[24] One study with 189 lung cancer patients found that treatment delay resulted in poorer prognosis for patients,[25] whilst another study with 132 patients found that longer specialist treatment delay does not result in poorer prognosis.[26] An aforementioned article also observed that most previous studies in different countries were monocentric studies and that it is difficult to decide which study is most reliable with regards to whether treatment delay affects patient survival rates.[4]

Most studies show no relationship between time-to-chemotherapy (TTC) and their survival rate.[27] However, it should be noted that in these review articles, the number of cases collected is generally very low, with the highest number of patients only 10,583.[27] Another study showed time intervals from diagnosis to treatment were not associated with survival outcomes in NSCLC.[28] In this previous study, they discussed NSCLC patients with different treatment such as surgery, radiotherapy, systemic therapy and palliative care which were not discussed in our study. They also suggested that delays to treatment might impact on other outcomes other than survival. However, there were only 1,729 patients in this previous study.[28] In summary, the majority of previous studies into whether treatment delay affects survival rate in non-small cell lung cancer patients lack large-scale nationwide statistical data. This can easily lead to bias and produce divergent conclusions. In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest

nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and IV).

In addition, detailed examination of the literature found that a decreased treatment delay increases the risk of death in patients; the explanation provided for this is that a shorter treatment delay may mean that the patients have more obvious or more severe symptoms.[24] Therefore, there is a need to correct the result with cancer stage and severity.[24] A previous study has also suggested that a shorter treatment delay may reflect a requirement for more urgent treatment due to severity of symptoms, resulting in a poor prognosis.[29] Therefore, in this paper, we also considered the effects of cancer stage on treatment delay and patient prognosis. In another paper, it was also mentioned that the definition of treatment delay should be more standardized and accurate.[4] Another paper mentioned that it is not easy to accurately calculate the time of treatment initiation.[24] In addition, the calculation of patient delay (from symptom to doctor) is also prone to errors. Therefore, in this study, our definition of treatment delay was made according to the cancer registration archives and NHI database, from pathological diagnosis confirmation until treatment initiation.

For cancer patients in general, current medical guidelines all recommend early diagnosis and treatment to improve patient prognosis. However, early diagnosis is

difficult due to multiple factors, such as non-apparent symptoms and patient delay. However, in this study, we found that if the interval from confirmation of pathological diagnosis to treatment initiation in non-small cell lung cancer patients is shortened to 7 days, this can effectively improve their 5-year survival rate (improvements of 0.49-9.07% were observed, according to the different stages of lung cancer). We also found that this improvement in 5-year survival rate was particularly marked for non-small cell lung cancer patients at early stages (stage I and II), at 10.28-10.34%. However, in late stage (stage III and stage IV) patients, the 5-year survival rate was only increased by 1.91% and 0.49%. It is extremely ambitious for lung cancer treatment to commence within 7 days of diagnosis considering the staging exam taking time. This group in the study (< 7 days to treatment) may be skewed towards those whose cancer was diagnosed at the time or surgery. A previous study showed that NSCLC growth rate appeared to be highly variable and related to histological subtype which was not discussed in our study.[30] Doubling times can be quite variable in different stages of NSCLC. Another study showed that rapid tumor progression was noted in patients with untreated, predominantly stage III NSCLC.[31] In our study, table 4 shows stage III non-small cell lung cancer patients with the interval from diagnosis to treatment initiation more than 60 days had significantly higher relative risk of death than patients with an interval ≤7 days (HR: 1.13, 95% CI: 1.06-1.21). This may be due to rapid tumor

progression characteristics of stage III NSCLC. However, the delay treatment effect is not significant in stage IV NSCLC patients, which may be associated with poor outcome and low survival rate in late stage of NSCLC. Therefore, we recommended that in future policies, treatment recommendations should be formulated so that patients can start treatment within 7 days after pathological diagnosis confirmation of non-small cell lung cancer to increase their 5-year survival rate. This is particularly important for early stage (stage I and II) non-small cell lung cancer patients, where improvement effects are more significant.

In this study, we also found that the effect of the interval from diagnosis to treatment initiation and patient survival rate decreased with more advanced cancer stages. Therefore, in patients who have stage I (HR: 1.45-2.41) or stage II (HR: 1.21-1.58) cancer, the longer the interval from diagnosis to treatment initiation, the higher the risk of death in patients. However, in stage III patients, compared with patients with an interval from diagnosis to treatment initiation ≤7 days, only when the interval from diagnosis to treatment initiation was ≥ 61 days was the risk of death increased. However, the magnitude of the increased risk of death is lower than in stage I and II patients (HR: 1.03-1.06). Therefore, this study found that timely treatment of stage I and II lung cancer patients has greater benefits. Therefore, we recommend that we should shorten the interval from diagnosis to treatment initiation especially in stage I and II lung cancer

patients, thus decreasing the risk of death and improving prognosis. However, due to data limitation, we used crude survival instead of disease free survival.

In recent studies, it was found that patients with oral cancers who underwent MDT treatment had significantly higher survival rates, and that the proportion of patients who underwent treatment was higher than those who did not joining MDT.[32] Previous studies have shown that the use of MDT care in cancer treatment can improve patient prognosis.[33] This is particularly the case in head and neck cancers, where MDT care is not only cost-effective but can also improve survival rates.[34] Previous studies have shown that in lung cancer patients MDT care can significantly improve the patient's acceptance of treatment, but does not significantly improve patient survival rates.[33] In this study, we found that patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

In summary, this study recommends that the interval from diagnosis to treatment initiation should be minimized during treatment of lung cancer patients at various cancer stages, particularly in stage I and II patients. In addition, in stage III and stage IV patients, we recommend the addition of MDT care to decrease the risk of death and improve prognosis.

Limitations

A secondary random database derived from the National Health Insurance Research Database was employed for this study. The information on individual lifestyle, health behaviors, which may also affect the result, is not available. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is not available in our database, and disease free survival is also not available in our study.

Conclusions

In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and stage IV) with pathological confirmation. NSCLC patients with timeliness treatment in stage I and II have better survival rate than others.

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Competing interests

The authors declare that they have no competing interests.

Author's contribution

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Funding acquisition: Pei-Tseng Kung, Wen-Chen Tsai

Patient consent form

As this study used anonymized secondary data retrieved from the Taiwan's National Health Insurance Research Database, the requirement for informed consent was waived by the ethics committee.

Data sharing

This study used the National Health Insurance Research Database published by the Ministry of Health, Taiwan. Due to legal restrictions imposed by the Taiwan government related to the Personal Information Protection Act, the database cannot be made publicly available. All researchers can apply for using the databases for conducting their studies. Requests for data can be sent as a formal proposal to the Science Center of the Ministry of Health and Welfare (http://www.mohw.gov.tw/EN/Ministry/Index.aspx). Any raw data are not allowed to be brought out from the Science Center. Only the analytic outputs in format of table or figure can be printed out. The restrictions prohibited the authors from making the minimal data set publicly available.

Figure Legend

Figure 1. Adjusted survival curve in lung cancer patients with different cancer stages

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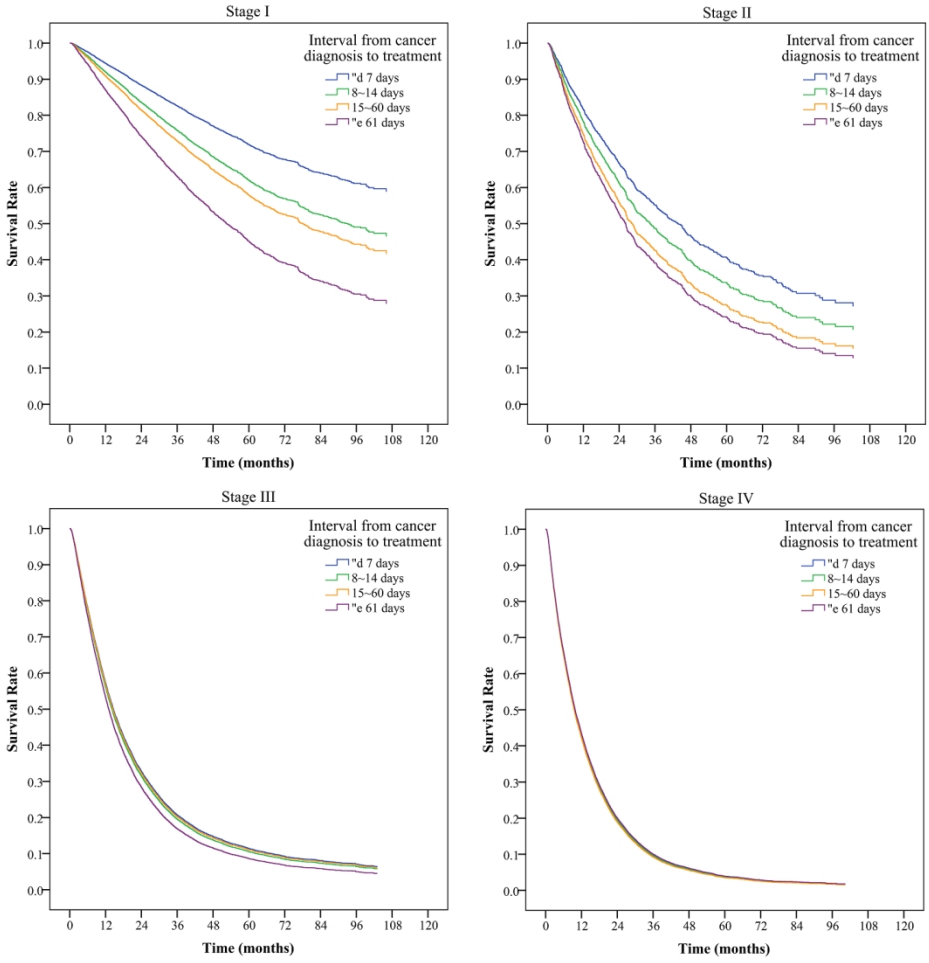

Figure 1

67x67mm (600 x 600 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			**5-6**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			**6-10**
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,9
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-19
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-19
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			20-26
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

Running head: Treatment delay and survival for non-small cell lung cancer

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Abstract

OBJECTIVES. This study aimed to determine if treatment delay after non-small cell lung cancer (NSCLC) diagnosis impacts patient survival rate.

STUDY DESIGN. This study is a natural experiment in Taiwan. A retrospective cohort investigation was conducted from 2004 to 2010, which included 42,962 patients with newly diagnosed NSCLC.

METHODS. We identified 42,962 patients with newly diagnosed NSCLC in the Taiwan Cancer Registry from 2004 to 2010. We calculated the time interval between diagnosis and treatment initiation. All patients were followed from the index date to death, or the end of 2012. Cox proportional hazard models were used to examine the relationship between mortality and time interval.

RESULTS. We included 42,962 patients (15,799 men and 27,163 women) with newly diagnosed NSCLC. The mortality rate exhibited a significantly positive correlation to time interval from cancer diagnosis to treatment initiation. The adjusted hazard ratios ranged from 1.04 to 1.08 in all subgroups time interval more than 7 days compared with the counterpart subgroup of the interval from cancer diagnosis to treatment ≤7 days. The trend was also noted regardless of the patients with lung cancer in stage I, stage II, and stage III.

CONCLUSIONS. There is a major association between time to treat and mortality of patients with NSCLC, especially in stages I and II. We suggest that efforts should be made to

minimize the interval from diagnosis to treatment while further study is ongoing to determine causation.

Strengths and limitations of this study

- It consisted of nationwide patients with non-small cell lung cancer.
- We collected nationwide data from 42,962 non-small cell lung cancer patients, which is the largest nationwide study to date.
- There were very few studies investigating treatment delay effects on the reduction of survival rate of lung cancer patients.
- Our lung cancer stages (stages I, II, III, and IV) were based on pathological confirmation.
- Information on patients' quantitative lung function and need for provocative cardiac testing are not available and may be significant factors determining the time to treat interval.

Keywords: lung cancer; non-small cell lung cancer; delay treatment; timeliness of treatment; survival

INTRODUCTION

Lung cancer is among the most common causes of cancer death, particularly in industrialized countries.[1] In addition, the incidence of lung cancer has been gradually increasing over the last 50 years,[2] becoming a worldwide public health issue.[3] Lung cancer can be classified into small cell lung cancer and non-small cell lung cancer, of which the latter accounts for 80% of all lung cancer cases.[4] Despite recent improvements in treatment, the prognosis for lung cancer patients is still poor. Regardless of whether a patient has non-small cell lung cancer or small cell lung cancer, the 5-year survival rate is only 17.4%.[2 5-7] Most lung cancers are in the late stage (stages IIIB or IV) when diagnosed, which is likely to be a result of the long interval between the onset of symptoms and diagnosis.[8] There are often large differences in the length of the interval from the first appearance of symptoms to confirmation of diagnosis and treatment initiation in these patients.[4] Although there were many relevant studies on whether differences in the time delay between diagnosis to treatment initiation affects the prognosis of lung cancer patients, no definitive conclusion has been reached.[4] An increasing number of relevant studies have also highlighted the importance of this topic.

In Taiwan, 99.68% of the populace is covered by National Healthcare Insurance (NHI) program. Under this system, lung cancer is classified as a catastrophic illness and is exempt from treatment-related fees, thereby that patients are not affected by economic factor. According to 2016 statistics from the Taiwan Ministry of Health and Welfare, cancer has

consistently been the top cause of death. Among various types of cancer, lung cancer ranks first in the cause of death, with a mortality rate of 39.9 per 100,000 people. Therefore, it is important for public health providers to improve lung cancer prognoses and increase survival rates. The Taiwan Cancer Registry (TCR), a population-based cancer registry, was founded in 1979. The registry is organized by the Ministry of Health and Welfare. The Taiwan Cancer Registry Database (TCRD) records data of all types of cancer diagnosed and treatments in patients in Taiwan. The completeness (97%) and data quality of the Cancer Registry Database has achieved at an excellent level.[9] The accuracy of NHIRD has been validated in previous studies.[10] This study aims to utilize national large-scale statistical data to investigate whether the interval between lung cancer diagnosis and treatment affects survival rate; concurrently, we also aim to examine the impact of other relevant factors on survival. This will provide a reference for future treatment for lung cancer patients of improving their survival.

METHODS

Data sources and participants

We included 55,014 newly diagnosed non-small cell lung cancer patients from 2004 to 2010. The newly diagnosed non-small cell lung cancer patients were defined as ICD-O-3 with C339 to C349 without any cancers before. Then we excluded those lung cancer patients with unknown stage for 3,993 patients. We also excluded lung cancer patients in situ (70 patients), with multiple cancer (1,298 patients), palliative treatment at the beginning (1,934 patients),

mortality before lung cancer diagnosed (64 patients), personal characteristics data missing (109 patients), and hospital data missing (4,584 patients). In our study, patients with multiple cancers may affect survival due to other cancer effect. In Taiwan, palliative treatment is coded as special code in NHIRD. Non-small cell lung cancer patients with palliative treatment at beginning may be due to patients refusing further treatment or not receiving aggressive treatment. We excluded them for informal treatment. Otherwise, we also excluded those patients with data missing for accuracy. Finally, we had 42,962 people.

The data for this study was obtained from the Taiwan Cancer Registry, which was used to acquire study participants. We also linked this data to the National Health Insurance Database and the Cause of Death File from 2002 to 2012 that was provided by the Ministry of Health and Welfare. The accuracy of Taiwan Cancer Registry and NHIRD has achieved at an excellent level.

Patient and public involvement

No patients were involved in the planning, conception and design of this study, as this study was based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan.

Variable descriptions

In this study, with regards to the variables used, the general characteristics of lung cancer patients included sex and age. Age was defined as the age at which the patient had a

confirmatory diagnosis by pathology. The financial status of the patient was based on their monthly salary. The degree of urbanization at the patient's place of residence was used to represent environmental factors. The level of urbanization was based on 7 levels of classification from highly urbanized developed cities (level 1) to remote areas (level 7). The health status of the patient included data on whether the patient had other catastrophic illnesses besides cancer, their Charlson Comorbidity Index (CCI), and the stage of non-small cell lung cancer. The definition of catastrophic illness was based on the 30 types of catastrophic illnesses or injuries as defined by the National Health Insurance Administration, which include stroke, chronic kidney failure, systemic lupus erythematosus, type I diabetes and severe mental illness. The degree of comorbidity was classified into three levels based on the CCI [11]. Tumor staging was based on the guidelines of the American Joint Committee on Cancer (6th edition for tumors diagnosed from 2004-2009, 7th edition for tumors diagnosed in 2010), which includes stages I, II, III, and IV. Hospital attributes include the level of hospital (medical centers, regional hospitals, district hospitals, and others), hospital ownership (public or private institutions), and the volume of hospital services (low, medium, high) in treatment of non-small cell lung cancer patients. The volume of hospital services was divided into low, medium, and high on the basis of quartiles: service volumes of <25%, 25-75% and >75% were defined as low, medium and high, respectively. Patients were considered to be enrolled in multidisciplinary team (MDT) care if they received MDT treatment after pathological diagnosis of non-small cell lung cancer;

the definition of MDT is based on patients who were declared MDT treatment fees in the NHI database (47079B). The interval between diagnosis of non-small cell lung cancer and treatment initiation was defined as the period between pathological sectioning and diagnosis of non-small cell lung cancer after biopsy to the time when the patient underwent their first treatment (including surgery, radiotherapy, or chemotherapy). The operating definition of relevant treatments is based on the relevant treatment code that was declared in the NHI database, which was checked against the treatment registration information in the Taiwan Cancer Information Database.

Main outcome measurements

The main outcome examined in this study was the survival rate of lung cancer patients. Confirmation of death was based on patient data from the NHI database and this was compared with the Taiwan Cause of Death archives for confirmation.

Statistical analysis

We employed descriptive statistics to show general characteristics, financial status, environmental factors, health status of patients, hospital attributes, enrolment in MDT and the distribution status of the interval from diagnosis confirmation to treatment initiation in lung cancer patients who had a confirmatory diagnosis by pathology from 2004 to 2010. Following this, bivariate analysis was performed using the log-rank test to investigate whether there were significant differences between survival status by the end of 2012 and the interval from

diagnosis to treatment initiation. We then used univariate Cox proportional hazards regression to analyze relevant prognostic factors that affect the survival of lung cancer patients. The adjusted Cox proportional hazards model was used to investigate the relative risk of survival of lung cancer patients with different cancer stages with different intervals from diagnosis confirmation to treatment initiation, after controlling for related variables. Independent variables included patient characteristics, financial status, environmental factors, health status, hospital attributes, enrolment in MDT, and grouping of time to treatment initiation. The dependent variable was survival. Lastly, after controlling for relevant variables, the adjusted Cox proportional hazards model was used to generate survival curves for lung cancer patients of various stages and with different interval periods.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). A P value <0.05 was regarded as statistically significant and all tests were two-sided.

RESULTS

Descriptive statistics of lung cancer patient characteristics for different treatment intervals

In all lung cancer patients, the mean 5-year survival rate was 17.61%. As the interval from diagnosis to treatment initiation increased, the 5-year survival rate decreased from 26.12% to 6.02% (Table 1). We also included time to treatment with 0 day (TTT=0) cases in the <7 days group in our study. There were 7,363 cases with TTT=0 accounting for 17.14% of all patients

in our study. We had 3,258 females accounting for 44.25% in this subgroup. The age of diagnosed in most patients was from 65-74 years old accounting for 28.28% with mean age of 64.67 years old. The treatment of most patients with TTT=0 was surgery combining with radiotherapy and chemotherapy. The 5-year survival rate was 34.9% in this group with TTT=0.

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Total number	42,962	100.00	15,769	36.70	9,296	21.64	12,510	29.12	5,387	12.54	-
Five-year survival rate	42,962	17.61	15,769	26.12	9,296	15.96	12,510	12.99	5,387	6.02	<0.001
Gender											<0.001
Female	15,799	36.77	6,154	38.95	3,235	20.48	4,419	27.97	1,991	12.60	
Male	27,163	63.23	9,615	35.40	6,061	22.31	8,091	29.79	3,396	12.50	
Age											<0.001
≤ 44	2,106	4.90	889	42.21	455	21.60	568	26.97	194	9.21	
45~54	5,686	13.23	2,375	41.77	1,263	22.21	1,549	27.24	499	8.78	
55~64	9,155	21.31	3,634	39.69	2,033	22.21	2,658	29.03	830	9.07	
65~74	12,659	29.47	4,548	35.93	2,801	22.13	3,819	30.17	1,491	11.78	
≥ 75	13,356	31.09	4,323	32.37	2,744	20.55	3,916	29.32	2,373	17.77	
Mean age (m, sd)	66.76	12.44	65.52	12.55	66.45	12.22	67.04	12.15	70.25	12.46	<0.001
Monthly salary											<0.001
Low-income	461	1.07	137	29.72	101	21.91	154	33.41	69	14.97	
≤ 17280	1,475	3.43	542	36.75	311	21.08	447	30.31	175	11.86	
17281~22800	22,935	53.38	8,074	35.20	5,079	22.15	6,751	29.44	3,031	13.22	
22801~28800	8,069	18.78	2,961	36.70	1,690	20.94	2,376	29.45	1,042	12.91	
28801~36300	2,676	6.23	1,011	37.78	588	21.97	782	29.22	295	11.02	
36301~45800	3,280	7.63	1,333	40.64	689	21.01	923	28.14	335	10.21	
≥ 45801	4,066	9.46	1,711	42.08	838	20.61	1,077	26.49	440	10.82	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Urbanization											0.186
Level 1	11,759	27.37	4,335	36.87	2,494	21.21	3,404	28.95	1,526	12.98	
Level 2	12,117	28.20	4,506	37.19	2,615	21.58	3,527	29.11	1,469	12.12	
Level 3	6,523	15.18	2,334	35.78	1,424	21.83	1,946	29.83	819	12.56	
Level 4	6,795	15.82	2,518	37.06	1,506	22.16	1,974	29.05	797	11.73	
Level 5	1,524	3.55	523	34.32	338	22.18	439	28.81	224	14.70	
Level 6	2,217	5.16	807	36.40	490	22.10	627	28.28	293	13.22	
Level 7	2,027	4.72	746	36.80	429	21.16	593	29.26	259	12.78	
CCI score											<0.001
≤ 3	20,388	47.46	7,475	36.66	4,576	22.44	6,186	30.34	2,151	10.55	
4~6	7,587	17.66	2,761	36.39	1,646	21.70	2,218	29.23	962	12.68	
≥ 7	14,987	34.88	5,533	36.92	3,074	20.51	4,106	27.40	2,274	15.17	
Other catastrophic illness											<0.001
No	41,474	96.54	15,300	36.89	8,984	21.66	12,076	29.12	5,114	12.33	
Yes	1,488	3.46	469	31.52	312	20.97	434	29.17	273	18.35	
Cancer stage											<0.001
Stage I	5,681	13.22	3,226	56.79	910	16.02	1,269	22.34	276	4.86	
Stage II	1,526	3.55	589	38.60	338	22.15	462	30.28	137	8.98	
Stage III	11,696	27.22	4,030	34.46	2,843	24.31	3,500	29.92	1,323	11.31	
Stage IV	24,059	56.00	7,924	32.94	5,205	21.63	7,279	30.25	3,651	15.18	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
MDT care											<0.001
No	37,716	87.79	13,669	36.24	8,012	21.24	10,974	29.10	5,061	13.42	
Yes	5,246	12.21	2,100	40.03	1,284	24.48	1,536	29.28	326	6.21	
Hospital level											<0.001
Medical centers	29,228	68.03	11,075	37.89	6,452	22.07	8,427	28.83	3,274	11.20	
Regional hospitals	12,601	29.33	4,395	34.88	2,655	21.07	3,787	30.05	1,764	14.00	
District hospitals	1,014	2.36	261	25.74	178	17.55	279	27.51	296	29.19	
Others	119	0.28	38	31.93	11	9.24	17	14.29	53	44.54	
Hospital ownership											<0.001
Public	16,770	39.03	6,619	39.47	3,776	22.52	4,558	27.18	1,817	10.83	
Private	26,192	60.97	9,150	34.93	5,520	21.08	7,952	30.36	3,570	13.63	
Hospital services volume											<0.001
Low	10,807	25.15	3,905	36.13	2,177	20.14	2,935	27.16	1,790	16.56	
Middle	21,043	48.98	7,519	35.73	4,652	22.11	6,486	30.82	2,386	11.34	
High	11,112	25.86	4,345	39.10	2,467	22.20	3,089	27.80	1,211	10.90	

[a] Log-rank test

Five-year survival rate of patients for different treatment intervals

At the same time, we found that in stage I patients, the 5-year survival rate decreased by 9.07% due to delayed treatment (patients with intervals >7 days). In stage

II patients, if patients started treatment earlier (interval ≤7 days), their 5-year survival rate increased by 9.01%. Early treatment (interval ≤7 days) was found to have a smaller effect on 5-year survival rate in stage III and stage IV patients, with an increase in 5-year survival rate of 1.91% and 0.49% (Table 2).

Table 2. Five-year survival rate of patients for different treatment intervals

Variables	Stage I		Stage II		Stage III		Stage IV		P value [a]
	N	%	N	%	N	%	N	%	
Total number	5,681	61.61	1,526	34.41	11,696	12.95	24,059	5.11	
Interval from cancer diagnosis to treatment									<0.001
≤ 7 days	3,226	70.68	589	43.42	4,030	14.86	7,924	5.60	
8~14 days	910	60.58	338	33.74	2,843	12.11	5,205	4.58	
15~60 days	1,269	49.07	462	29.81	3,500	13.81	7,279	5.43	
≥ 61 days	276	21.10	137	14.56	1,323	6.83	3,651	4.12	

[a] Log-rank test

The effect of different treatment intervals on mortality risk in patients with lung cancer

Table 3 shows that when the group with interval from cancer diagnosis to treatment ≤7 days was used as a reference, the adjusted HR for mortality in other groups (8-14 days, 15-60 days, and ≥61 days) was significantly increased with increasing interval time (HR: 1.04-1.08). Among patients at various cancer stages, using stage I patients as a control group, the adjusted HRs for mortality for cancer patients at various stages was significantly higher (HR: 2.06-5.89) and the more advanced the cancer stages, the higher the adjusted HR for mortality. Patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

Table 3. Relative risk of death in patients for different treatment intervals

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Interval from cancer diagnosis to treatment						
≤ 7 days (ref.)						
8~14 days	**1.26**	<0.001	**1.04**	1.01	1.07	0.004
15~60 days	**1.30**	<0.001	**1.06**	1.04	1.09	<0.001
≥ 61 days	**1.66**	<0.001	**1.08**	1.04	1.11	<0.001
Gender						
Female (ref.)						
Male	**1.54**	<0.001	**1.50**	1.47	1.53	<0.001
Age						
≤ 44 (ref.)						
45~54	**0.97**	0.357	**0.97**	0.92	1.03	0.351
55~64	**1.02**	0.478	**1.03**	0.97	1.09	0.331
65~74	**1.63**	<0.001	**1.27**	1.21	1.34	<0.001
≥ 75	**1.93**	<0.001	**1.79**	1.69	1.88	<0.001
Monthly salary						
Low-income (ref.)						
≤ 17280	**0.72**	<0.001	**0.89**	0.80	1.00	0.049
17281~22800	**0.81**	<0.001	**0.86**	0.78	0.95	0.002
22801~28800	**0.74**	<0.001	**0.83**	0.75	0.91	<0.001
28801~36300	**0.60**	<0.001	**0.79**	0.71	0.87	<0.001
36301~45800	**0.59**	<0.001	**0.78**	0.70	0.87	<0.001

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
≥ 45801	**0.56**	<0.001	**0.73**	0.66	0.81	<0.001
Urbanization level						
Level 1 (ref.)						
Level 2	**1.07**	<0.001	**0.99**	0.96	1.02	0.523
Level 3	**1.20**	<0.001	**1.04**	1.00	1.07	0.036
Level 4	**1.21**	<0.001	**1.01**	0.98	1.05	0.596
Level 5	**1.33**	<0.001	**1.01**	0.95	1.08	0.671
Level 6	**1.39**	<0.001	**1.09**	1.04	1.15	0.001
Level 7	**1.25**	<0.001	**1.02**	0.96	1.07	0.570
CCI score						
≤ 3 (ref.)						
4~6	**1.35**	<0.001	**1.18**	1.14	1.21	<0.001
≥ 7	**1.80**	<0.001	**1.28**	1.25	1.31	<0.001
Other catastrophic illness						
No (ref.)						
Yes	**1.25**	<0.001	**1.26**	1.19	1.33	<0.001
Cancer stage						
Stage I (ref.)						
Stage II	**2.29**	<0.001	**2.06**	1.91	2.23	<0.001
Stage III	**4.48**	<0.001	**3.94**	3.75	4.13	<0.001
Stage IV	**6.51**	<0.001	**5.89**	5.62	6.17	<0.001
MDT care						
No (ref.)						

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Yes	**0.95**	0.001	**0.91**	0.88	0.94	<0.001
Hospital level						
Medical centers (ref.)						
Regional hospitals	**1.28**	<0.001	**0.99**	0.96	1.02	0.347
District hospitals	**2.06**	<0.001	**1.25**	1.17	1.34	<0.001
Others	**1.17**	0.137	**0.90**	0.73	1.10	0.286
Hospital ownership						
Public (ref.)						
Private	**1.27**	<0.001	**1.13**	1.10	1.16	<0.001
Hospital services volume						
Low (ref.)						
Middle	**0.72**	<0.001	**0.83**	0.81	0.85	<0.001
High	**0.59**	<0.001	**0.71**	0.68	0.74	<0.001

[a] Cox proportional hazards regression

The effect of different treatment intervals on mortality risk in patients with lung cancer at different cancer stages

Table 4 shows that in stage I lung cancer patients, with patients with intervals of ≤7 days as the reference group, as the interval increased, the relative risk of death also significantly increased (HR: 1.45-2.41). This was also true for stage II (HR: 1.21-1.58) and the intervals more than 60 days of stage III lung cancer patients (HR: 1.13, 95% CI: 1.06-1.21). In stage IV patients, using patients with an interval ≤7 days as a

reference group, the relative risk of death was without significantly difference. Figure 1 shows adjusted survival curve in lung cancer patients with different cancer stages.

Table 4. Relative risk of death in patients for different treatment intervals and at different cancer stages

Variables	Stage I [a]			Stage II [a]			Stage III [a]			Stage IV [a]		
	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]
Interval from cancer diagnosis to treatment												
≤ 7 days (ref.)												
8~14 days	**1.45**	1.28 1.64	<0.001	**1.21**	1.01 1.45	0.039	**1.04**	0.98 1.09	0.177	**0.99**	0.95 1.03	0.561
15~60 days	**1.66**	1.49 1.84	<0.001	**1.44**	1.22 1.69	<0.001	**1.02**	0.97 1.07	0.560	**1.01**	0.98 1.04	0.572
≥ 61 days	**2.41**	2.06 2.83	<0.001	**1.58**	1.26 1.97	<0.001	**1.13**	1.06 1.21	<0.001	**0.98**	0.94 1.02	0.249

a. Patient age, gender, monthly salary, level of urbanization of place of residence, CCI score, other illness, MDT care, hospital level, hospital ownership, and hospital services volume were all controlled for using various models.

[b] adjusted Cox proportional hazards model

DISCUSSION

We found that the mortality rate exhibited significantly positive correlation to time interval from cancer diagnosis to treatment initiation in all stage NSCLC patients. The ratio of male to female in our study is similar to that in previous studies.[12 13] The delays between diagnosis and treatment can be categorized into three stages: namely, patient delay, diagnosis delay, and treatment delay.[2] Of all studies which investigated treatment delays in lung cancer patients, the study with the largest number of patients included 54,338 patients, but was limited to non-metastatic lung cancer patients.[12] In addition, the study only focused on patients who underwent surgical excision and did not analyze the treatment delay status and associated factors for all lung cancer patients. Another study collected data from 28,732 patients to investigate whether treatment delay affects survival rate.[14] The researchers found that if the interval from diagnosis to treatment was within 35 days, then there is improved survival for patients with localized disease, reduced survival for those with distant disease, but didn't have significant effect on patients with regional disease.[14] However, in that study, the diagnosis to treatment interval was divided into just two groups (<35 days and >35 days), which makes it more difficult to show the correlation between different treatment delay groups and patient survival rates. In addition, in that study, the authors did not investigate whether different treatment delay periods affect survival rate for different cancer stages as they only

classified cancers as localized, regional, or distant. To the best of our knowledge, the current study is the first large-scale nationwide study that examines whether treatment delay in non-small cell lung cancer affects patient survival rate. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate for different cancer stages (stages I, II, III and IV).

Previous studies have observed that if patients are older, have more comorbidities, or have stage I cancer, they are more likely to delay treatment (interval from diagnosis to treatment >30 days).[12] Similar findings were observed in our study: for patients aged ≥55 years, the greater the age the greater the proportion with treatment delay (interval ≥61 days) (Table 1). Patients with high CCI scores also demonstrated significantly increased proportions in treatment delay (interval ≥61 days) (Table 1). CCI is a general score to evaluate patients' comorbidity and does not focus on lung cancer patients. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is more accurate for evaluating their severity but is not available in our study. It is a fact that patients with poorer lung function require additional testing to determine candidacy for surgery. This testing, including six minute walk test, quantitative perfusion scans, cardiopulmonary exercise testing and consultation with pulmonary medicine takes time and is not available in our study. However, during analysis of the correlation between treatment

delay and lung cancer stage, we found that the proportion of stage I patients with treatment delay was significantly lower than patients with other stages of lung cancer. A previous study has observed that in non-small cell lung cancer patients, treatment delay is not associated with cancer stage.[15],[16-20] In contrast, treatment delay had more serious effects in stage III and IV patients.[21] However, in our study, we found that the proportion of stage I patients with treatment delay (interval from diagnosis to treatment ≥61 days) was significantly lower (4.86%, $p<0.001$), when compared with patients at other stages.

Previous studies have mentioned that in non-small cell lung cancer patients, our understanding of the effects of diagnosis and treatment delay on the prognosis of patients is limited, although an increasing number of recent studies are emphasizing the importance of this topic.[4] Some studies have found that in patients with a symptom-to-treatment interval (STI) of >60 days, the survival rate was significantly higher than that of patients with a STI of <60 days.[22] However, if patients were further divided on the basis of the type of lung cancer, this difference was only significant in NSCLC patients.[22] However, the number of patients included in this study was only 103 (96 men).[23] Two other studies, with 378 and 410 patients each, found that delaying diagnosis and treatment did not affect patient survival rates.[16] [17] Another study of 466 non-small cell lung cancer patients found that patients with shorter STIs had lower

survival rates.[24] One study with 189 lung cancer patients found that treatment delay resulted in poorer prognosis for patients,[25] whilst another study with 132 patients found that longer specialist treatment delay does not result in poorer prognosis.[26] An aforementioned article also observed that most previous studies in different countries were monocentric studies and that it is difficult to decide which study is most reliable with regards to whether treatment delay affects patient survival rates.[4]

Most studies show no relationship between time-to-chemotherapy (TTC) and their survival rate.[27] However, it should be noted that in these review articles, the number of cases collected is generally very low, with the highest number of patients only 10,583.[27] Another study showed time intervals from diagnosis to treatment were not associated with survival outcomes in NSCLC.[28] In this previous study, they discussed NSCLC patients with different treatment such as surgery, radiotherapy, systemic therapy and palliative care which were not discussed in our study. They also suggested that delays to treatment might impact on other outcomes other than survival. However, there were only 1,729 patients in this previous study.[28] In summary, the majority of previous studies into whether treatment delay affects survival rate in non-small cell lung cancer patients lack large-scale nationwide statistical data. This can easily lead to bias and produce divergent conclusions. In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest

nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and IV).

In addition, detailed examination of the literature found that a decreased treatment delay increases the risk of death in patients; the explanation provided for this is that a shorter treatment delay may mean that the patients have more obvious or more severe symptoms.[24] Therefore, there is a need to correct the result with cancer stage and severity.[24] A previous study has also suggested that a shorter treatment delay may reflect a requirement for more urgent treatment due to severity of symptoms, resulting in a poor prognosis.[29] Therefore, in this paper, we also considered the effects of cancer stage on treatment delay and patient prognosis. In another paper, it was also mentioned that the definition of treatment delay should be more standardized and accurate.[4] Another paper mentioned that it is not easy to accurately calculate the time of treatment initiation.[24] In addition, the calculation of patient delay (from symptom to doctor) is also prone to errors. Therefore, in this study, our definition of treatment delay was made according to the cancer registration archives and NHI database, from pathological diagnosis confirmation until treatment initiation.

For cancer patients in general, current medical guidelines all recommend early diagnosis and treatment to improve patient prognosis. However, early diagnosis is

difficult due to multiple factors, such as non-apparent symptoms and patient delay. However, in this study, we found that if the interval from confirmation of pathological diagnosis to treatment initiation in non-small cell lung cancer patients is shortened to 7 days, this can effectively improve their 5-year survival rate (improvements of 0.49-9.07% were observed, according to the different stages of lung cancer). We also found that this improvement in 5-year survival rate was particularly marked for non-small cell lung cancer patients at early stages (stage I and II), at 10.28-10.34%. However, in late stage (stage III and stage IV) patients, the 5-year survival rate was only increased by 1.91% and 0.49%. It is extremely ambitious for lung cancer treatment to commence within 7 days of diagnosis considering the staging exam taking time. This group in the study (< 7 days to treatment) may be skewed towards those whose cancer was diagnosed at the time or surgery. A previous study showed that NSCLC growth rate appeared to be highly variable and related to histological subtype which was not discussed in our study.[30] Doubling times can be quite variable in different stages of NSCLC. Another study showed that rapid tumor progression was noted in patients with untreated, predominantly stage III NSCLC.[31] In our study, table 4 shows stage III non-small cell lung cancer patients with the interval from diagnosis to treatment initiation more than 60 days had significantly higher relative risk of death than patients with an interval ≤7 days (HR: 1.13, 95% CI: 1.06-1.21). This may be due to rapid tumor

progression characteristics of stage III NSCLC. However, the delay treatment effect is not significant in stage IV NSCLC patients, which may be associated with poor outcome and low survival rate in late stage of NSCLC. Therefore, we recommended that in future policies, treatment recommendations should be formulated so that patients can start treatment within 7 days after pathological diagnosis confirmation of non-small cell lung cancer to increase their 5-year survival rate. This is particularly important for early stage (stage I and II) non-small cell lung cancer patients, where improvement effects are more significant.

In this study, we also found that the effect of the interval from diagnosis to treatment initiation and patient survival rate decreased with more advanced cancer stages. Therefore, in patients who have stage I (HR: 1.45-2.41) or stage II (HR: 1.21-1.58) cancer, the longer the interval from diagnosis to treatment initiation, the higher the risk of death in patients. However, in stage III patients, compared with patients with an interval from diagnosis to treatment initiation ≤7 days, only when the interval from diagnosis to treatment initiation was ≥ 61 days was the risk of death increased. However, the magnitude of the increased risk of death is lower than in stage I and II patients (HR: 1.03-1.06). Therefore, this study found that timely treatment of stage I and II lung cancer patients has greater benefits. Therefore, we recommend that we should shorten the interval from diagnosis to treatment initiation especially in stage I and II lung cancer

patients, thus decreasing the risk of death and improving prognosis. However, due to data limitation, we used crude survival instead of disease free survival.

In recent studies, it was found that patients with oral cancers who underwent MDT treatment had significantly higher survival rates, and that the proportion of patients who underwent treatment was higher than those who did not joining MDT.[32] Previous studies have shown that the use of MDT care in cancer treatment can improve patient prognosis.[33] This is particularly the case in head and neck cancers, where MDT care is not only cost-effective but can also improve survival rates.[34] Previous studies have shown that in lung cancer patients MDT care can significantly improve the patient's acceptance of treatment, but does not significantly improve patient survival rates.[33] In this study, we found that patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

In summary, this study identifies an association between time to treat and survival in NSCLC. Although causation is not definitive, efforts to diminish time to treat in the lung cancer patient would seem prudent while awaiting further study on the issue. In addition, in stage III and stage IV patients, we recommend the addition of MDT care to decrease the risk of death and improve prognosis.

Limitations

A secondary random database derived from the National Health Insurance Research Database was employed for this study. The information on individual lifestyle, health behaviors, which may also affect the result, is not available. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is not available in our database, and disease free survival is also not available in our study.

Conclusions

In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and stage IV) with pathological confirmation. Treatment timeliness is associated with better survival rates in patients with NSCLC, particularly stage I and II.

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Competing interests

The authors declare that they have no competing interests.

Author's contribution

Conceptualization: Chang-Hung Tsai, Pei-Tseng Kung, Wen-Chen Tsai

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Supervision: Wen-Chen Tsai

Project administration: Chang-Hung Tsai, Wei-Yin Kuo, Pei-Tseng Kung

Funding acquisition: Pei-Tseng Kung, Wen-Chen Tsai

Patient consent form

As this study used anonymized secondary data retrieved from the Taiwan's National Health Insurance Research Database, the requirement for informed consent was waived by the ethics committee.

Data sharing

This study used the National Health Insurance Research Database published by the Ministry of Health, Taiwan. Due to legal restrictions imposed by the Taiwan government related to the Personal Information Protection Act, the database cannot be made publicly available. All researchers can apply for using the databases for conducting their studies. Requests for data can be sent as a formal proposal to the Science Center of the Ministry of Health and Welfare (http://www.mohw.gov.tw/EN/Ministry/Index.aspx). Any raw data are not allowed to be brought out from the Science Center. Only the analytic outputs in format of table or figure can be printed out. The restrictions prohibited the authors from making the minimal data set publicly available.

Figure Legend

Figure 1. Adjusted survival curve in lung cancer patients with different cancer stages

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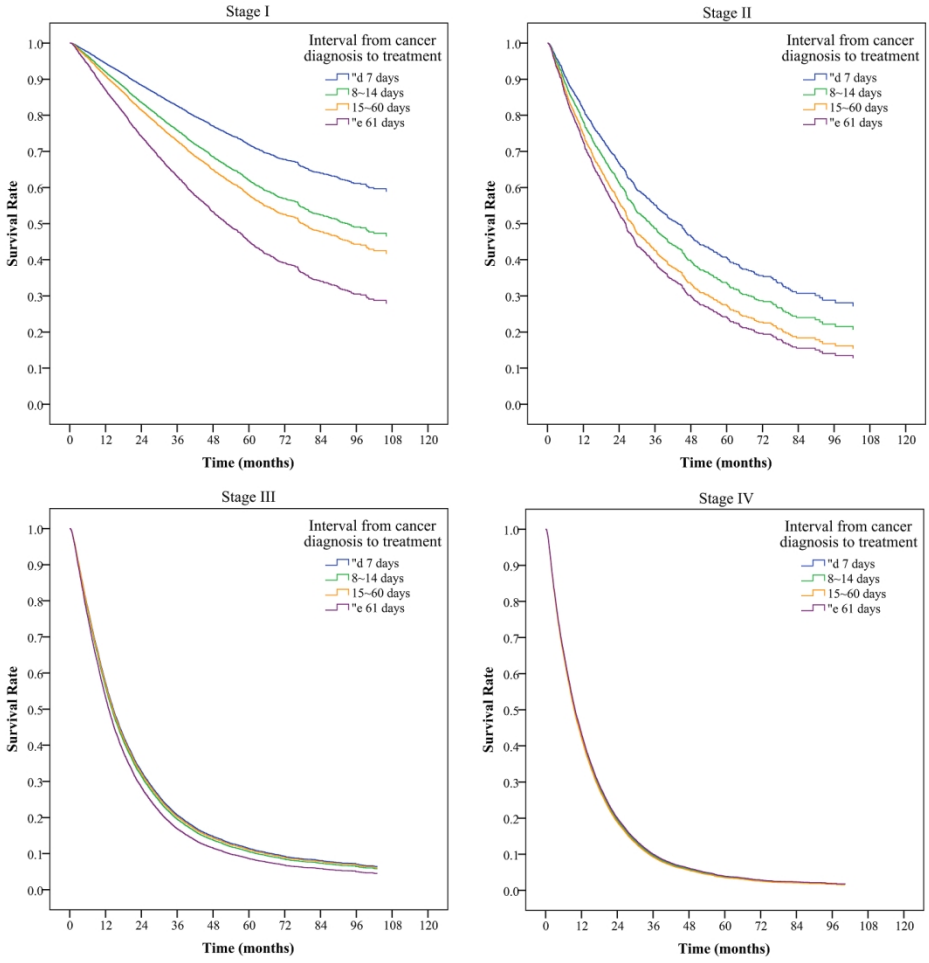

Figure 1

67x67mm (600 x 600 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			**5-6**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			**6-10**
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,9
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-19
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-19
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			20-26
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

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Effect of time interval from diagnosis to treatment for non-small cell lung cancer on survival: A national cohort study in Taiwan

Running head: Treatment delay and survival for non-small cell lung cancer

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Abstract

OBJECTIVES. This study aimed to determine if treatment delay after non-small cell lung cancer (NSCLC) diagnosis impacts patient survival rate.

STUDY DESIGN. This study is a natural experiment in Taiwan. A retrospective cohort investigation was conducted from 2004 to 2010, which included 42,962 patients with newly diagnosed NSCLC.

METHODS. We identified 42,962 patients with newly diagnosed NSCLC in the Taiwan Cancer Registry from 2004 to 2010. We calculated the time interval between diagnosis and treatment initiation. All patients were followed from the index date to death, or the end of 2012. Cox proportional hazard models were used to examine the relationship between mortality and time interval.

RESULTS. We included 42,962 patients (15,799 men and 27,163 women) with newly diagnosed NSCLC. The mortality rate exhibited a significantly positive correlation to time interval from cancer diagnosis to treatment initiation. The adjusted hazard ratios ranged from 1.04 to 1.08 in all subgroups time interval more than 7 days compared with the counterpart subgroup of the interval from cancer diagnosis to treatment ≤7 days. The trend was also noted regardless of the patients with lung cancer in stage I, stage II, and stage III.

CONCLUSIONS. There is a major association between time to treat and mortality of patients with NSCLC, especially in stages I and II. We suggest that efforts should be made to

minimize the interval from diagnosis to treatment while further study is ongoing to determine causation.

Strengths and limitations of this study

- It consisted of nationwide patients with non-small cell lung cancer.
- We collected nationwide data from 42,962 non-small cell lung cancer patients, which is the largest nationwide study to date.
- There were very few studies investigating treatment delay effects on the reduction of survival rate of lung cancer patients.
- Our lung cancer stages (stages I, II, III, and IV) were based on pathological confirmation.
- Information on patients' quantitative lung function and need for provocative cardiac testing are not available and may be significant factors determining the time to treat interval.

Keywords: lung cancer; non-small cell lung cancer; delay treatment; timeliness of treatment; survival

INTRODUCTION

Lung cancer is among the most common causes of cancer death, particularly in industrialized countries.[1] In addition, the incidence of lung cancer has been gradually increasing over the last 50 years,[2] becoming a worldwide public health issue.[3] Lung cancer can be classified into small cell lung cancer and non-small cell lung cancer, of which the latter accounts for 80% of all lung cancer cases.[4] Despite recent improvements in treatment, the prognosis for lung cancer patients is still poor. Regardless of whether a patient has non-small cell lung cancer or small cell lung cancer, the 5-year survival rate is only 17.4%.[2 5-7] Most lung cancers are in the late stage (stages IIIB or IV) when diagnosed, which is likely to be a result of the long interval between the onset of symptoms and diagnosis.[8] There are often large differences in the length of the interval from the first appearance of symptoms to confirmation of diagnosis and treatment initiation in these patients.[4] Although there were many relevant studies on whether differences in the time delay between diagnosis to treatment initiation affects the prognosis of lung cancer patients, no definitive conclusion has been reached.[4] An increasing number of relevant studies have also highlighted the importance of this topic.

In Taiwan, 99.68% of the populace is covered by National Healthcare Insurance (NHI) program. Under this system, lung cancer is classified as a catastrophic illness and is exempt from treatment-related fees, thereby that patients are not affected by economic factor.

According to 2016 statistics from the Taiwan Ministry of Health and Welfare, cancer has consistently been the top cause of death. Among various types of cancer, lung cancer ranks first in the cause of death, with a mortality rate of 39.9 per 100,000 people. Therefore, it is important for public health providers to improve lung cancer prognoses and increase survival rates. The Taiwan Cancer Registry (TCR), a population-based cancer registry, was founded in 1979. The registry is organized by the Ministry of Health and Welfare. The Taiwan Cancer Registry Database (TCRD) records data of all types of cancer diagnosed and treatments in patients in Taiwan. The completeness (97%) and data quality of the Cancer Registry Database has achieved at an excellent level.[9] The accuracy of NHIRD has been validated in previous studies.[10] This study aims to utilize national large-scale statistical data to investigate whether the interval between lung cancer diagnosis and treatment affects survival rate; concurrently, we also aim to examine the impact of other relevant factors on survival. This will provide a reference for future treatment for lung cancer patients of improving their survival.

METHODS

Data sources and participants

We included 55,014 newly diagnosed non-small cell lung cancer patients from 2004 to 2010. The newly diagnosed non-small cell lung cancer patients were defined as ICD-O-3 with C339 to C349 without any cancers before. Then we excluded those lung cancer patients

with unknown stage for 3,993 patients. We also excluded lung cancer patients in situ (70 patients), with multiple cancer (1,298 patients), palliative treatment at the beginning (1,934 patients), mortality before lung cancer diagnosed (64 patients), personal characteristics data missing (109 patients), and hospital data missing (4,584 patients). In our study, patients with multiple cancers may affect survival due to other cancer effect. In Taiwan, palliative treatment is coded as special code in NHIRD. Non-small cell lung cancer patients with palliative treatment at beginning may be due to patients refusing further treatment or not receiving aggressive treatment. We excluded them for informal treatment. Otherwise, we also excluded those patients with data missing for accuracy. Finally, we had 42,962 people.

The data for this study was obtained from the Taiwan Cancer Registry, which was used to acquire study participants. We also linked this data to the National Health Insurance Database and the Cause of Death File from 2002 to 2012 that was provided by the Ministry of Health and Welfare. The accuracy of Taiwan Cancer Registry and NHIRD has achieved at an excellent level.

Patient and public involvement

No patients were involved in the planning, conception and design of this study, as this study was based on the National Health Insurance Research Database, published by the Ministry of Health and Welfare, Taiwan.

Variable descriptions

In this study, with regards to the variables used, the general characteristics of lung cancer patients included sex and age. Age was defined as the age at which the patient had a confirmatory diagnosis by pathology. The financial status of the patient was based on their monthly salary. The degree of urbanization at the patient's place of residence was used to represent environmental factors. The level of urbanization was based on 7 levels of classification from highly urbanized developed cities (level 1) to remote areas (level 7). The health status of the patient included data on whether the patient had other catastrophic illnesses besides cancer, their Charlson Comorbidity Index (CCI), and the stage of non-small cell lung cancer. The definition of catastrophic illness was based on the 30 types of catastrophic illnesses or injuries as defined by the National Health Insurance Administration, which include stroke, chronic kidney failure, systemic lupus erythematosus, type I diabetes and severe mental illness. The degree of comorbidity was classified into three levels based on the CCI [11]. Tumor staging was based on the guidelines of the American Joint Committee on Cancer (6th edition for tumors diagnosed from 2004-2009, 7th edition for tumors diagnosed in 2010), which includes stages I, II, III, and IV. Hospital attributes include the level of hospital (medical centers, regional hospitals, district hospitals, and others), hospital ownership (public or private institutions), and the volume of hospital services (low, medium, high) in treatment of non-small cell lung cancer patients. The volume of hospital services was divided into low, medium, and high on the basis of quartiles: service volumes of <25%, 25-75% and >75%

were defined as low, medium and high, respectively. Patients were considered to be enrolled in multidisciplinary team (MDT) care if they received MDT treatment after pathological diagnosis of non-small cell lung cancer; the definition of MDT is based on patients who were declared MDT treatment fees in the NHI database (47079B). The interval between diagnosis of non-small cell lung cancer and treatment initiation was defined as the period between pathological sectioning and diagnosis of non-small cell lung cancer after biopsy to the time when the patient underwent their first treatment (including surgery, radiotherapy, or chemotherapy). The operating definition of relevant treatments is based on the relevant treatment code that was declared in the NHI database, which was checked against the treatment registration information in the Taiwan Cancer Information Database.

Main outcome measurements

The main outcome examined in this study was the survival rate of lung cancer patients. Confirmation of death was based on patient data from the NHI database and this was compared with the Taiwan Cause of Death archives for confirmation.

Statistical analysis

We employed descriptive statistics to show general characteristics, financial status, environmental factors, health status of patients, hospital attributes, enrolment in MDT and the distribution status of the interval from diagnosis confirmation to treatment initiation in lung cancer patients who had a confirmatory diagnosis by pathology from 2004 to 2010.

Following this, bivariate analysis was performed using the log-rank test to investigate whether there were significant differences between survival status by the end of 2012 and the interval from diagnosis to treatment initiation. We then used univariate Cox proportional hazards regression to analyze relevant prognostic factors that affect the survival of lung cancer patients. The adjusted Cox proportional hazards model was used to investigate the relative risk of survival of lung cancer patients with different cancer stages with different intervals from diagnosis confirmation to treatment initiation, after controlling for related variables. Independent variables included patient characteristics, financial status, environmental factors, health status, hospital attributes, enrolment in MDT, and grouping of time to treatment initiation. The dependent variable was survival. Lastly, after controlling for relevant variables, the adjusted Cox proportional hazards model was used to generate survival curves for lung cancer patients of various stages and with different interval periods.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC). A P value <0.05 was regarded as statistically significant and all tests were two-sided.

RESULTS

Descriptive statistics of lung cancer patient characteristics for different treatment intervals

In all lung cancer patients, the mean 5-year survival rate was 17.61%. As the interval from diagnosis to treatment initiation increased, the 5-year survival rate decreased from

26.12% to 6.02% (Table 1). We also included time to treatment with 0 day (TTT=0) cases in the <7 days group in our study. There were 7,363 cases with TTT=0 accounting for 17.14% of all patients in our study. We had 3,258 females accounting for 44.25% in this subgroup. The age of diagnosed in most patients was from 65-74 years old accounting for 28.28% with mean age of 64.67 years old. The treatment of most patients with TTT=0 was surgery combining with radiotherapy and chemotherapy. The 5-year survival rate was 34.9% in this group with TTT=0.

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Total number	42,962	100.00	15,769	36.70	9,296	21.64	12,510	29.12	5,387	12.54	-
Five-year survival rate	42,962	17.61	15,769	26.12	9,296	15.96	12,510	12.99	5,387	6.02	<0.001
Gender											<0.001
Female	15,799	36.77	6,154	38.95	3,235	20.48	4,419	27.97	1,991	12.60	
Male	27,163	63.23	9,615	35.40	6,061	22.31	8,091	29.79	3,396	12.50	
Age											<0.001
≤ 44	2,106	4.90	889	42.21	455	21.60	568	26.97	194	9.21	
45~54	5,686	13.23	2,375	41.77	1,263	22.21	1,549	27.24	499	8.78	
55~64	9,155	21.31	3,634	39.69	2,033	22.21	2,658	29.03	830	9.07	
65~74	12,659	29.47	4,548	35.93	2,801	22.13	3,819	30.17	1,491	11.78	
≥ 75	13,356	31.09	4,323	32.37	2,744	20.55	3,916	29.32	2,373	17.77	
Mean age (m, sd)	66.76	12.44	65.52	12.55	66.45	12.22	67.04	12.15	70.25	12.46	<0.001
Monthly salary											<0.001
Low-income	461	1.07	137	29.72	101	21.91	154	33.41	69	14.97	
≤ 17280	1,475	3.43	542	36.75	311	21.08	447	30.31	175	11.86	
17281~22800	22,935	53.38	8,074	35.20	5,079	22.15	6,751	29.44	3,031	13.22	
22801~28800	8,069	18.78	2,961	36.70	1,690	20.94	2,376	29.45	1,042	12.91	
28801~36300	2,676	6.23	1,011	37.78	588	21.97	782	29.22	295	11.02	
36301~45800	3,280	7.63	1,333	40.64	689	21.01	923	28.14	335	10.21	
≥ 45801	4,066	9.46	1,711	42.08	838	20.61	1,077	26.49	440	10.82	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
Urbanization											0.186
Level 1	11,759	27.37	4,335	36.87	2,494	21.21	3,404	28.95	1,526	12.98	
Level 2	12,117	28.20	4,506	37.19	2,615	21.58	3,527	29.11	1,469	12.12	
Level 3	6,523	15.18	2,334	35.78	1,424	21.83	1,946	29.83	819	12.56	
Level 4	6,795	15.82	2,518	37.06	1,506	22.16	1,974	29.05	797	11.73	
Level 5	1,524	3.55	523	34.32	338	22.18	439	28.81	224	14.70	
Level 6	2,217	5.16	807	36.40	490	22.10	627	28.28	293	13.22	
Level 7	2,027	4.72	746	36.80	429	21.16	593	29.26	259	12.78	
CCI score											<0.001
≤ 3	20,388	47.46	7,475	36.66	4,576	22.44	6,186	30.34	2,151	10.55	
4~6	7,587	17.66	2,761	36.39	1,646	21.70	2,218	29.23	962	12.68	
≥ 7	14,987	34.88	5,533	36.92	3,074	20.51	4,106	27.40	2,274	15.17	
Other catastrophic illness											<0.001
No	41,474	96.54	15,300	36.89	8,984	21.66	12,076	29.12	5,114	12.33	
Yes	1,488	3.46	469	31.52	312	20.97	434	29.17	273	18.35	
Cancer stage											<0.001
Stage I	5,681	13.22	3,226	56.79	910	16.02	1,269	22.34	276	4.86	
Stage II	1,526	3.55	589	38.60	338	22.15	462	30.28	137	8.98	
Stage III	11,696	27.22	4,030	34.46	2,843	24.31	3,500	29.92	1,323	11.31	
Stage IV	24,059	56.00	7,924	32.94	5,205	21.63	7,279	30.25	3,651	15.18	

Table 1. Bivariate analysis of lung cancer patient characteristics for different treatment intervals (continued)

Variables	Total		Interval from cancer diagnosis to treatment								P value[a]
			≤ 7 days		8~14 days		15~60 days		≥ 61 days		
	N	%	N	%	N	%	N	%	N	%	
MDT care											<0.001
No	37,716	87.79	13,669	36.24	8,012	21.24	10,974	29.10	5,061	13.42	
Yes	5,246	12.21	2,100	40.03	1,284	24.48	1,536	29.28	326	6.21	
Hospital level											<0.001
Medical centers	29,228	68.03	11,075	37.89	6,452	22.07	8,427	28.83	3,274	11.20	
Regional hospitals	12,601	29.33	4,395	34.88	2,655	21.07	3,787	30.05	1,764	14.00	
District hospitals	1,014	2.36	261	25.74	178	17.55	279	27.51	296	29.19	
Others	119	0.28	38	31.93	11	9.24	17	14.29	53	44.54	
Hospital ownership											<0.001
Public	16,770	39.03	6,619	39.47	3,776	22.52	4,558	27.18	1,817	10.83	
Private	26,192	60.97	9,150	34.93	5,520	21.08	7,952	30.36	3,570	13.63	
Hospital services volume											<0.001
Low	10,807	25.15	3,905	36.13	2,177	20.14	2,935	27.16	1,790	16.56	
Middle	21,043	48.98	7,519	35.73	4,652	22.11	6,486	30.82	2,386	11.34	
High	11,112	25.86	4,345	39.10	2,467	22.20	3,089	27.80	1,211	10.90	

[a] Log-rank test

Five-year survival rate of patients for different treatment intervals

At the same time, we found that in stage I patients, the 5-year survival rate decreased by 9.07% due to delayed treatment (patients with intervals >7 days). In

stage II patients, if patients started treatment earlier (interval ≤7 days), their 5-year survival rate increased by 9.01%. Early treatment (interval ≤7 days) was found to have a smaller effect on 5-year survival rate in stage III and stage IV patients, with an increase in 5-year survival rate of 1.91% and 0.49% (Table 2).

Table 2. Five-year survival rate of patients for different treatment intervals

Variables	Stage I		Stage II		Stage III		Stage IV		P value [a]
	N	%	N	%	N	%	N	%	
Total number	5,681	61.61	1,526	34.41	11,696	12.95	24,059	5.11	
Interval from cancer diagnosis to treatment									<0.001
≤ 7 days	3,226	70.68	589	43.42	4,030	14.86	7,924	5.60	
8~14 days	910	60.58	338	33.74	2,843	12.11	5,205	4.58	
15~60 days	1,269	49.07	462	29.81	3,500	13.81	7,279	5.43	
≥ 61 days	276	21.10	137	14.56	1,323	6.83	3,651	4.12	

[a] Log-rank test

The effect of different treatment intervals on mortality risk in patients with lung cancer

Table 3 shows that when the group with interval from cancer diagnosis to treatment ≤7 days was used as a reference, the adjusted HR for mortality in other groups (8-14 days, 15-60 days, and ≥61 days) was significantly increased with increasing interval time (HR: 1.04-1.08). Among patients at various cancer stages, using stage I patients as a control group, the adjusted HRs for mortality for cancer patients at various stages was significantly higher (HR: 2.06-5.89) and the more advanced the cancer stages, the higher the adjusted HR for mortality. Patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

Table 3. Relative risk of death in patients for different treatment intervals

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Interval from cancer diagnosis to treatment						
≤ 7 days (ref.)						
8~14 days	**1.26**	<0.001	**1.04**	1.01	1.07	0.004
15~60 days	**1.30**	<0.001	**1.06**	1.04	1.09	<0.001
≥ 61 days	**1.66**	<0.001	**1.08**	1.04	1.11	<0.001
Gender						
Female (ref.)						
Male	**1.54**	<0.001	**1.50**	1.47	1.53	<0.001
Age						
≤ 44 (ref.)						
45~54	**0.97**	0.357	**0.97**	0.92	1.03	0.351
55~64	**1.02**	0.478	**1.03**	0.97	1.09	0.331
65~74	**1.63**	<0.001	**1.27**	1.21	1.34	<0.001
≥ 75	**1.93**	<0.001	**1.79**	1.69	1.88	<0.001
Monthly salary						
Low-income (ref.)						
≤ 17280	**0.72**	<0.001	**0.89**	0.80	1.00	0.049
17281~22800	**0.81**	<0.001	**0.86**	0.78	0.95	0.002
22801~28800	**0.74**	<0.001	**0.83**	0.75	0.91	<0.001
28801~36300	**0.60**	<0.001	**0.79**	0.71	0.87	<0.001
36301~45800	**0.59**	<0.001	**0.78**	0.70	0.87	<0.001

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
≥ 45801	**0.56**	<0.001	**0.73**	0.66	0.81	<0.001
Urbanization level						
Level 1 (ref.)						
Level 2	**1.07**	<0.001	**0.99**	0.96	1.02	0.523
Level 3	**1.20**	<0.001	**1.04**	1.00	1.07	0.036
Level 4	**1.21**	<0.001	**1.01**	0.98	1.05	0.596
Level 5	**1.33**	<0.001	**1.01**	0.95	1.08	0.671
Level 6	**1.39**	<0.001	**1.09**	1.04	1.15	0.001
Level 7	**1.25**	<0.001	**1.02**	0.96	1.07	0.570
CCI score						
≤ 3 (ref.)						
4~6	**1.35**	<0.001	**1.18**	1.14	1.21	<0.001
≥ 7	**1.80**	<0.001	**1.28**	1.25	1.31	<0.001
Other catastrophic illness						
No (ref.)						
Yes	**1.25**	<0.001	**1.26**	1.19	1.33	<0.001
Cancer stage						
Stage I (ref.)						
Stage II	**2.29**	<0.001	**2.06**	1.91	2.23	<0.001
Stage III	**4.48**	<0.001	**3.94**	3.75	4.13	<0.001
Stage IV	**6.51**	<0.001	**5.89**	5.62	6.17	<0.001
MDT care						
No (ref.)						

Variables	Unadjusted		Adjusted			
	HR	P value	HR	95% CI		P value [a]
Yes	**0.95**	0.001	**0.91**	0.88	0.94	<0.001
Hospital level						
Medical centers (ref.)						
Regional hospitals	**1.28**	<0.001	**0.99**	0.96	1.02	0.347
District hospitals	**2.06**	<0.001	**1.25**	1.17	1.34	<0.001
Others	**1.17**	0.137	**0.90**	0.73	1.10	0.286
Hospital ownership						
Public (ref.)						
Private	**1.27**	<0.001	**1.13**	1.10	1.16	<0.001
Hospital services volume						
Low (ref.)						
Middle	**0.72**	<0.001	**0.83**	0.81	0.85	<0.001
High	**0.59**	<0.001	**0.71**	0.68	0.74	<0.001

[a] Cox proportional hazards regression

The effect of different treatment intervals on mortality risk in patients with lung cancer at different cancer stages

Table 4 shows that in stage I lung cancer patients, with patients with intervals of ≤7 days as the reference group, as the interval increased, the relative risk of death also significantly increased (HR: 1.45-2.41). This was also true for stage II (HR: 1.21-1.58) and the intervals more than 60 days of stage III lung cancer patients (HR: 1.13, 95% CI: 1.06-1.21). In stage IV patients, using patients with an interval ≤7 days

as a reference group, the relative risk of death was without significantly difference. Figure 1 shows adjusted survival curve in lung cancer patients with different cancer stages.

Table 4. Relative risk of death in patients for different treatment intervals and at different cancer stages

Variables	Stage I [a]			Stage II [a]			Stage III [a]			Stage IV [a]		
	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]	HR	95% CI	P value [b]
Interval from cancer diagnosis to treatment												
≤ 7 days (ref.)												
8~14 days	**1.45**	1.28 1.64	<0.001	**1.21**	1.01 1.45	0.039	**1.04**	0.98 1.09	0.177	**0.99**	0.95 1.03	0.561
15~60 days	**1.66**	1.49 1.84	<0.001	**1.44**	1.22 1.69	<0.001	**1.02**	0.97 1.07	0.560	**1.01**	0.98 1.04	0.572
≥ 61 days	**2.41**	2.06 2.83	<0.001	**1.58**	1.26 1.97	<0.001	**1.13**	1.06 1.21	<0.001	**0.98**	0.94 1.02	0.249

a. Patient age, gender, monthly salary, level of urbanization of place of residence, CCI score, other illness, MDT care, hospital level, hospital ownership, and hospital services volume were all controlled for using various models.

[b] adjusted Cox proportional hazards model

DISCUSSION

We found that the mortality rate exhibited significantly positive correlation to time interval from cancer diagnosis to treatment initiation in all stage NSCLC patients. The ratio of male to female in our study is similar to that in previous studies.[12 13] The delays between diagnosis and treatment can be categorized into three stages: namely, patient delay, diagnosis delay, and treatment delay.[2] Of all studies which investigated treatment delays in lung cancer patients, the study with the largest number of patients included 54,338 patients, but was limited to non-metastatic lung cancer patients.[12] In addition, the study only focused on patients who underwent surgical excision and did not analyze the treatment delay status and associated factors for all lung cancer patients. Another study collected data from 28,732 patients to investigate whether treatment delay affects survival rate.[14] The researchers found that if the interval from diagnosis to treatment was within 35 days, then there is improved survival for patients with localized disease, reduced survival for those with distant disease, but didn't have significant effect on patients with regional disease.[14] However, in that study, the diagnosis to treatment interval was divided into just two groups (<35 days and >35 days), which makes it more difficult to show the correlation between different treatment delay groups and patient survival rates. In addition, in that study, the authors did not investigate whether different treatment

delay periods affect survival rate for different cancer stages as they only classified cancers as localized, regional, or distant. To the best of our knowledge, the current study is the first large-scale nationwide study that examines whether treatment delay in non-small cell lung cancer affects patient survival rate. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate for different cancer stages (stages I, II, III and IV).

Previous studies have observed that if patients are older, have more comorbidities, or have stage I cancer, they are more likely to delay treatment (interval from diagnosis to treatment >30 days).[12] Similar findings were observed in our study: for patients aged ≥55 years, the greater the age the greater the proportion with treatment delay (interval ≥61 days) (Table 1). Patients with high CCI scores also demonstrated significantly increased proportions in treatment delay (interval ≥61 days) (Table 1). CCI is a general score to evaluate patients' comorbidity and does not focus on lung cancer patients. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is more accurate for evaluating their severity but is not available in our study. It is a fact that patients with poorer lung function require additional testing to determine candidacy for surgery. This testing, including six minute walk test, quantitative perfusion scans, cardiopulmonary exercise testing and consultation with

pulmonary medicine takes time and is not available in our study. However, during analysis of the correlation between treatment delay and lung cancer stage, we found that the proportion of stage I patients with treatment delay was significantly lower than patients with other stages of lung cancer. A previous study has observed that in non-small cell lung cancer patients, treatment delay is not associated with cancer stage.[15],[16-20] In contrast, treatment delay had more serious effects in stage III and IV patients.[21] However, in our study, we found that the proportion of stage I patients with treatment delay (interval from diagnosis to treatment ≥61 days) was significantly lower (4.86%, $p<0.001$), when compared with patients at other stages.

Previous studies have mentioned that in non-small cell lung cancer patients, our understanding of the effects of diagnosis and treatment delay on the prognosis of patients is limited, although an increasing number of recent studies are emphasizing the importance of this topic.[4] Some studies have found that in patients with a symptom-to-treatment interval (STI) of >60 days, the survival rate was significantly higher than that of patients with a STI of <60 days.[22] However, if patients were further divided on the basis of the type of lung cancer, this difference was only significant in NSCLC patients.[22] However, the number of patients included in this study was only 103 (96 men).[23] Two other studies, with 378 and 410 patients each, found that delaying diagnosis and treatment did not affect patient survival rates.[16 17]

Another study of 466 non-small cell lung cancer patients found that patients with shorter STIs had lower survival rates.[24] One study with 189 lung cancer patients found that treatment delay resulted in poorer prognosis for patients,[25] whilst another study with 132 patients found that longer specialist treatment delay does not result in poorer prognosis.[26] An aforementioned article also observed that most previous studies in different countries were monocentric studies and that it is difficult to decide which study is most reliable with regards to whether treatment delay affects patient survival rates.[4]

Most studies show no relationship between time-to-chemotherapy (TTC) and their survival rate.[27] However, it should be noted that in these review articles, the number of cases collected is generally very low, with the highest number of patients only 10,583.[27] Another study showed time intervals from diagnosis to treatment were not associated with survival outcomes in NSCLC.[28] In this previous study, they discussed NSCLC patients with different treatment such as surgery, radiotherapy, systemic therapy and palliative care which were not discussed in our study. They also suggested that delays to treatment might impact on other outcomes other than survival. However, there were only 1,729 patients in this previous study.[28] In summary, the majority of previous studies into whether treatment delay affects survival rate in non-small cell lung cancer patients lack large-scale nationwide

statistical data. This can easily lead to bias and produce divergent conclusions. In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and IV).

In addition, detailed examination of the literature found that a decreased treatment delay increases the risk of death in patients; the explanation provided for this is that a shorter treatment delay may mean that the patients have more obvious or more severe symptoms.[24] Therefore, there is a need to correct the result with cancer stage and severity.[24] A previous study has also suggested that a shorter treatment delay may reflect a requirement for more urgent treatment due to severity of symptoms, resulting in a poor prognosis.[29] Therefore, in this paper, we also considered the effects of cancer stage on treatment delay and patient prognosis. In another paper, it was also mentioned that the definition of treatment delay should be more standardized and accurate.[4] Another paper mentioned that it is not easy to accurately calculate the time of treatment initiation.[24] In addition, the calculation of patient delay (from symptom to doctor) is also prone to errors. Therefore, in this study, our definition of treatment delay was made according to the cancer registration archives and NHI database, from pathological diagnosis confirmation until treatment

initiation.

For cancer patients in general, current medical guidelines all recommend early diagnosis and treatment to improve patient prognosis. However, early diagnosis is difficult due to multiple factors, such as non-apparent symptoms and patient delay. However, in this study, we found that if the interval from confirmation of pathological diagnosis to treatment initiation in non-small cell lung cancer patients is shortened to 7 days, this is associated with an improvement in 5 year life expectancy (improvements of 0.49-9.07% were observed, according to the different stages of lung cancer). We also found that this improvement in 5-year survival rate was particularly marked for non-small cell lung cancer patients at early stages (stage I and II), at 10.28-10.34%. However, in late stage (stage III and stage IV) patients, the 5-year survival rate was only increased by 1.91% and 0.49%. It is extremely ambitious for lung cancer treatment to commence within 7 days of diagnosis considering the staging exam taking time. This group in the study (< 7 days to treatment) may be skewed towards those whose cancer was diagnosed at the time or surgery. A previous study showed that NSCLC growth rate appeared to be highly variable and related to histological subtype which was not discussed in our study.[30] Doubling times can be quite variable in different stages of NSCLC. Another study showed that rapid tumor progression was noted in patients with untreated, predominantly stage III NSCLC.[31]

In our study, table 4 shows stage III non-small cell lung cancer patients with the interval from diagnosis to treatment initiation more than 60 days had significantly higher relative risk of death than patients with an interval ≤7 days (HR: 1.13, 95% CI: 1.06-1.21). This may be due to rapid tumor progression characteristics of stage III NSCLC. However, the delay treatment effect is not significant in stage IV NSCLC patients, which may be associated with poor outcome and low survival rate in late stage of NSCLC. Therefore, we recommended that in future policies, treatment recommendations should be formulated so that patients can start treatment within 7 days after pathological diagnosis confirmation of non-small cell lung cancer to increase their 5-year survival rate. This is particularly important for early stage (stage I and II) non-small cell lung cancer patients, where improvement effects are more significant.

In this study, we also found that the effect of the interval from diagnosis to treatment initiation and patient survival rate decreased with more advanced cancer stages. Therefore, in patients who have stage I (HR: 1.45-2.41) or stage II (HR: 1.21-1.58) cancer, the longer the interval from diagnosis to treatment initiation, the higher the risk of death in patients. However, in stage III patients, compared with patients with an interval from diagnosis to treatment initiation ≤7 days, only when the interval from diagnosis to treatment initiation was ≥ 61 days was the risk of death

increased. However, the magnitude of the increased risk of death is lower than in stage I and II patients (HR: 1.03-1.06). It appears the association between time to treatment and outcome is stronger with lower stage disease. This may have implications on resource allocation specifically addressing the TTT phenomenon. Further study, however, is necessary to better understand causation.

In recent studies, it was found that patients with oral cancers who underwent MDT treatment had significantly higher survival rates, and that the proportion of patients who underwent treatment was higher than those who did not joining MDT.[32] Previous studies have shown that the use of MDT care in cancer treatment can improve patient prognosis.[33] This is particularly the case in head and neck cancers, where MDT care is not only cost-effective but can also improve survival rates.[34] Previous studies have shown that in lung cancer patients MDT care can significantly improve the patient's acceptance of treatment, but does not significantly improve patient survival rates.[33] In this study, we found that patients who underwent MDT care had a significantly lower adjusted HR for mortality compared with patients who did not (HR: 0.91, 95% CI: 0.88-0.94).

In summary, this study identifies an association between time to treat and survival in NSCLC. Although causation is not definitive, efforts to diminish time to treat in the lung cancer patient would seem prudent while awaiting further study on

the issue. In addition, in patients with NSCLC, we recommend the addition of MDT care to decrease the risk of death and improve prognosis.

Limitations

A secondary random database derived from the National Health Insurance Research Database was employed for this study. The information on individual lifestyle, health behaviors, which may also affect the result, is not available. The lung function testing such as forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO) is not available in our database, and disease free survival is also not available in our study.

Conclusions

In this study, we collected nationwide data from 42,962 non-small cell lung cancer patients, which, to the best of our knowledge, is the largest nationwide study to date. In addition, we also investigated the correlation between lung cancer treatment delay and survival rate in different cancer stages (stages I, II, III and stage IV) with pathological confirmation. Treatment timeliness is associated with better survival rates in patients with NSCLC, particularly stage I and II.

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Competing interests

The authors declare that they have no competing interests.

Author's contribution

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Software: Wen-Chen Tsai

Validation: Chang-Hung Tsai, Pei-Tseng Kung, Wen-Chen Tsai

Formal analysis: Chang-Hung Tsai, Wei-Yin Kuo

Data curation: Chang-Hung Tsai, Pei-Tseng Kung, Wen-Chen Tsai

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Supervision: Wen-Chen Tsai

Project administration: Chang-Hung Tsai, Wei-Yin Kuo, Pei-Tseng Kung

Funding acquisition: Pei-Tseng Kung, Wen-Chen Tsai

Patient consent form

As this study used anonymized secondary data retrieved from the Taiwan's National Health Insurance Research Database, the requirement for informed consent was waived by the ethics committee.

Data sharing

This study used the National Health Insurance Research Database published by the Ministry of Health, Taiwan. Due to legal restrictions imposed by the Taiwan government related to the Personal Information Protection Act, the database cannot be made publicly available. All researchers can apply for using the databases for conducting their studies. Requests for data can be sent as a formal proposal to the Science Center of the Ministry of Health and Welfare (http://www.mohw.gov.tw/EN/Ministry/Index.aspx). Any raw data are not allowed to be brought out from the Science Center. Only the analytic outputs in format of table or figure can be printed out. The restrictions prohibited the authors from making the

minimal data set publicly available.

Figure Legend

Figure 1. Adjusted survival curve in lung cancer patients with different cancer stages

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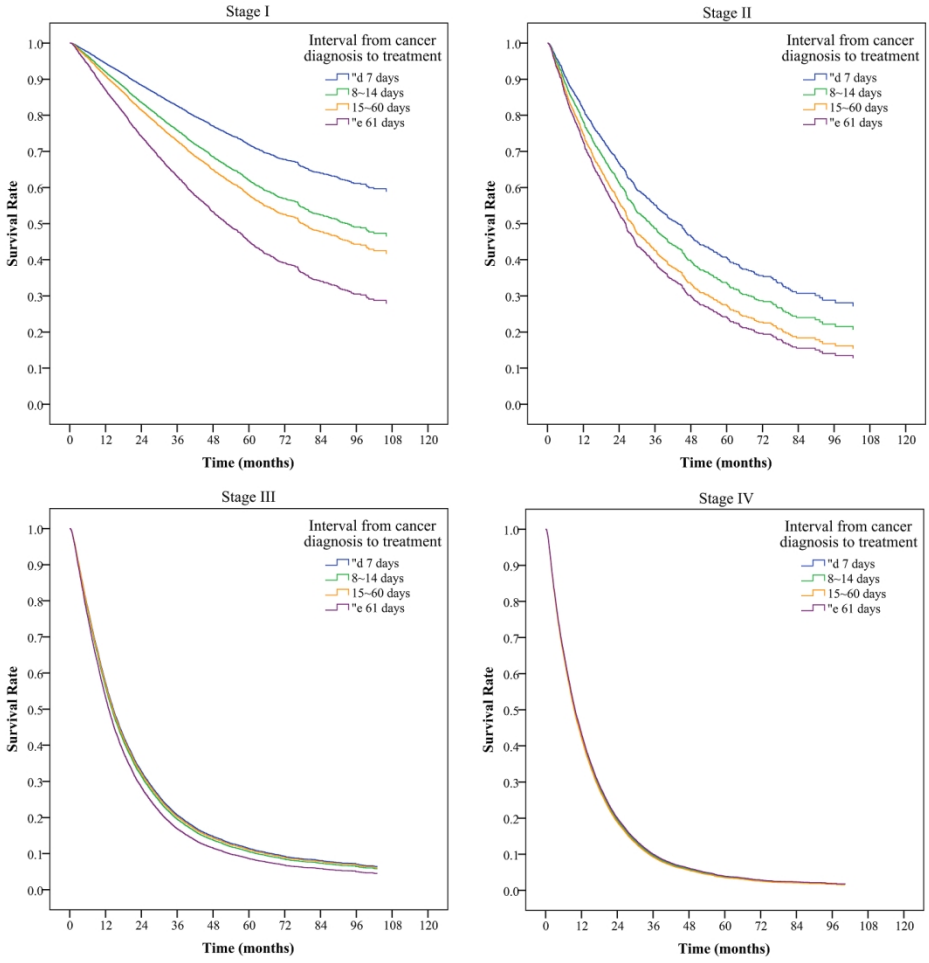

Figure 1

67x67mm (600 x 600 DPI)

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			**5-6**
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			**6-10**
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,9
Bias	9	Describe any efforts to address potential sources of bias	6-7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-19
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-19
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			20-26
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26-27
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.