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RISK FACTORS FOR NON–SMALL CELL LUNG CANCER MORTALITY IN PATIENTS ADMITTED AT THE LUNG CENTER OF THE PHILIPPINES: A RETROSPECTIVE COHORT FROM 2000 TO 2008

Sullian Sy–Naval, MD,[1] Vincent M. Balanag, Jr., MD,[1] Ruth DC. Babalo, MD,[1]
Corazon Adele F. Lavadia,[1] Maria Lourdes E. Amarillo, MPh[2]
[1]Lung Center of the Philippines
[2]University of the Philippines–Manila

ABSTRACT

Objectives. This study aimed to determine the survival and the risk factors associated with mortality of patients with non–small cell lung cancer (NSCLC) in a single institution.

Methodology. This was a retrospective cohort study involving patients with NSCLC admitted at the Lung Center of the Philippines (LCP) from 2000 to 2008.

Results. This study included 3,439 patients with NSCLC; 76% of whom were stage IIIB or higher at first admission. Survival time followed a generalized-gamma distribution with a median survival time of 121 days (25th and 75th percentile: 42 and 319 days, respectively). The patients diagnosed, received chemotherapy or radiotherapy at LCP was associated with higher survival. Poorer survival was observed among males, smokers, residents of the National Capital Region, patients with metastasis, previous surgery or radiotherapy elsewhere, and patients with pneumonia and COPD. The receipt of chemotherapy and diagnosis at an early stage showed the highest survival.

Conclusion. Among patients with NSCLC in this cohort, the median survival was four months. Receiving chemotherapy and diagnosis at an early stage yielded the highest probability of survival.

Keywords: survival, lung cancer, risk factors, non–small cell lung cancer, Philippines

Corresponding Author:
Vincent M. Balanag, Jr., MD
Lung Center of the Philippines
Email: vmbalanag@gmail.com

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INTRODUCTION

Lung cancer is one of the most common cancers among Filipinos, accounting for 12.2% of all cancer cases, second only to breast cancer, and is also the deadliest, the cause of 17.9% of all cancer deaths in 2018. The number of lung cancer cases are expected continue to increase and is predicted to reach 33,185 cases in 2040, almost double of cases recorded in 2018.[1] It also poses a huge economic burden to the country. Estimates of the total economic burden of lung cancer for the Philippines in 2015 was around 50,977 DALYs or disability adjusted life-years, mainly due to premature deaths.[2]

Over the past few decades, there has been significant progress in the management of lung cancer, including the introduction of national guidelines and polices, improvement in the diagnostic procedures and introduction of new treatments, with recent studies reporting a global trend towards improved survival in patients with lung cancer.[3-7]

Several studies have investigated the survival and prognostic factors of lung cancer patients in developing countries, with age, sex, stage, histopathology, performance status and treatment modalities showing varying effects on lung cancer survival.[8-10]

There is a paucity of data on the survival rates of lung cancer patients in the Philippines. Available data from Ngelangel et al. in 2002 showed one-year, three-year and five-year lung cancer survival rates of 27%, 11.1% and 7.2%, respectively.[11]

The present study aimed to describe survival rates and determine prognostic factors from the Lung Cancer Registry of the Lung Center of the Philippines, a national specialty center for lung and chest diseases where the biggest number of outpatient consultations and hospital admissions are due to patients with lung cancer. The findings hope to help clinicians in identifying strategies and modalities that may improve treatment outcomes and policy makers in improving access of patients to medical care and maximizing available resources for cancer care in the institution.

METHODOLOGY

Study design and setting

This was a retrospective cohort study among patients with non-small cell lung cancer (NSCLC) registered at the Lung Center of the Philippines.

Study Population

All histologically confirmed NSCLC diagnosed and/or treated at the Lung Center of the Philippines (LCP) between 2000-2008 were included. The patients with lung metastasis from other non-pulmonary malignancy and with missing and incomplete data were excluded in the survival analysis.

Data Collection

Only patients with histopathologically confirmed non-small cell carcinoma and staged according to the 7th edition of TNM staging were included in the study. Information on the clinico-demographic characteristics including smoking status, alcohol intake status, family history, co-morbidities, number of admissions, previous treatment elsewhere, site of metastasis, management (diagnostic procedure, supportive care, surgical resection, radiotherapy, chemotherapy and palliative care) and vital status of patients upon discharge were extracted from the chart. Diagnostic procedures include biopsy, computed tomographic (CT) scan, thoracentesis, thoracoscopy, cytology, thoracoscopy, mediastinoscopy, and thoracotomy. Supportive care consisted of blood transfusion, dialysis, intubation, mechanical ventilation, nasogastric tube insertion, oxygen inhalation and nutritional support. Information on re-admissions of the patients was also collected. Mortality of patients who were discharged alive in the last admission was verified at the National Statistics Office (NSO).

Data Handling and Analysis

Data were encoded via Epi InfoTM data entry program. Data quality assurance procedures were performed before analysis.

Descriptive statistics such as the mean and standard deviation of quantitative variables were computed. Frequency and percentage distribution of categorical variables were also obtained.

The distribution of the survival time of lung cancer patients was determined using the Easy Fit program. The association of survival time and each potential factor for mortality was determined using Eta and Pearson correlation coefficients in STATA software. All variables with significant correlation with survival time were considered in the multivariable survival analysis. Some variables which were not statistically significant but were known to have an association with survival time were considered in the survival model.

The explanatory variables assessed in the survival analysis were age, sex, residence, occupation, smoking status, co-existing illness, lung cancer stage, presence of metastasis, number of admissions, and management including diagnostic maneuvers and previous or on-site treatments. Time-varying covariates considered in the analysis were age, pneumonia, cancer stage, resective surgery, radiotherapy and chemotherapy. Variables significantly interacting with the main exposure variable "smoking status" as well as other possible interactions of variables were evaluated. Potential confounders were also assessed in the analysis.

Likelihood ratio tests were performed to determine the significance of the explanatory variables with survival time at 5% level of significance. Assessment of the goodness-of-fit of the model was done using the Bayesian Information Criterion (BIC). Randomness of censored observations was ascertained using method by David Kleinbaum.[12]

Definition of Outcomes

Survival time was defined as the difference between the beginning date (date of first admission as lung cancer case at LCP) and the end date (date of death for in-hospital mortality). For those discharged alive but later verified as mortality at the PSA-NSO, the reported date in the death certificate is the end date. For those discharged alive and could not be verified as mortality by the PSA-NSO were considered as censored observations.

RESULTS

A total of 3,439 diagnosed non-small cell lung cancer patients admitted from year 2000-2008 were included in the study.

Demographic Profile

Table 1 shows that most of the lung cancer patients were males (n=2,431; 70.7%) and married (n=2,724, 79.2%). The mean age was 60.3 years (SD=11.2) with the majority 60 years and above (n=1,868; 54.3%). More than 80% of the NSCLC patients seen at LCP resided in the National Capital Region, Regions III and IVA. The majority of the patients were farmers (n=429; 12.5%).

Table 1. *Frequency and percentage distribution of the demographic characteristics of lung cancer patients.*

Demographic Characteristics (n=3,439)	Frequency	Percentage
Sex		
Male	2,431	70.7
Female	1,008	29.3
Total	3,439	100.0
Age group (yrs)		
< 20	2	0.1
20-39	155	4.5
40-59	1,414	41.1
60 and above	1,868	54.3
Total	3,439	100.0
Civil Status		
Married	2724	79.2
Widow	455	13.2
Single	192	5.6
Separated	54	1.6
No information	14	0.4
Total	3,439	100.0
Top 3 Permanent Address (by regions)		
National Capital Region (NCR)	1,493	43.4
Region III-CENTRAL LUZON	755	22.0
Region IVA-CALABARZON	638	18.6
Most frequent occupations[a]		
Unspecified	670	19.5
Unemployed	558	16.2
Field crop farmers	429	12.5
Pensioner, retired or disabled	323	9.4
Motor vehicle drivers	230	6.7
Housewife	187	5.4

[a]The collected information on occupation was coded and grouped using the Philippine Standard Occupational and Classification of 2007 (PSOC 2007).

Medical History

Table 2 shows that current smokers accounted for about half of the cohort (n=1,725). The mean number of pack years was 42.6 (SD=35.2). 26.5% of patients were non-smokers. Less than half of cases reported any alcohol intake, with around 16% classified as alcohol drinkers. A family history of any malignancy was present in 24.7% (n=848). The most common co-existing illnesses were pulmonary tuberculosis (n=1,030; n=30%), hypertension (n=616; 17.9%), and pneumonia (n=520; 15.1%).

Table 2. *Frequency and percentage distribution of the history of lung cancer patients.*

History	Frequency	Percentage
Smoking status		
Smoker	1,725	50.2
Non-smoker	912	26.5
Ex-smoker	738	21.5
No information	46	1.3
Occasional smoker	18	0.5
TOTAL	3,439	100.0
Alcohol intake status		
Non-alcohol drinker	994	28.9
Occasional drinker	973	28.3
No information	657	19.1
Alcohol drinker	564	16.4
Previous alcohol drinker	251	7.3
TOTAL	3,439	100.0
Family history		
Hypertension	1,171	34.1
No Illness	927	27.0
Malignancy	848	24.7
PTB	726	21.1
Asthma	674	19.6
Co-existing illnesses		
No co-existing illness	1,130	32.9
Pulmonary tuberculosis	1,030	30.0
Hypertension	616	17.9
Pneumonia	520	15.1
COPD	423	12.3

Histologic Type, Cancer Stage and Treatment

Table 3 shows that the most common histologic type of non-small cell carcinoma was adenocarcinoma (n=1,648; 47.9%), followed by unspecified NSCLC (n=1,033; 30.0%), and squamous cell carcinoma (n=701; 20.4%). The majority of the patients were diagnosed in the advanced or metastatic stage of disease (n=2,977; 89.6%) on admission with only 13.1% (n=448) first seen in Stages I or II. Diagnostic procedures were performed in 79.3% (n=2,728), with resective surgery done in only 4.5% (n=155). Palliative care, chemotherapy and radiotherapy were provided in 30.4% (n=1,045), 24.8% (n=854) and 13.4% (n=459), respectively.

Table 3. *Frequency and percentage distribution of information on admission of lung cancer patients.*

Information on Admission	Frequency	Percentage
Histopathology:		
Adenocarcinoma	1,648	47.9
Unspecified NSCLC	1,033	30.0
Squamous	701	20.4
Large Cell	31	0.9
Adenosquamous	21	0.6
Others	5	0.1
Staging		
IA	15	0.4
IB	281	8.2
IIA	2	0.1
IIB	150	4.4
IIIA	391	11.4
IIIB	264	7.7
IVA	1,668	48.5
IVB	654	19.0
No Information	14	0.4
Total	3,439	100.0
Management		
Diagnostic	2,728	79.3
Palliative care	1,045	30.4
Chemotherapy	854	24.8
Supportive care	840	24.4
Radiotherapy	459	13.4
Resective surgery	155	4.5

Survival Analysis

About 72.2% of lung cancer patients in this study were recorded as mortality. The median survival time was 121 days or approximately 4 months. The incidence rate was 0.0038, which means that 38 people are expected to die of lung cancer per 10,000 person-days.

In the simple analysis, significant variable age was quadratic in nature but had no significant increase or decrease in the survival time per unit increase in age. Using the smoking status as an exposure variable for test for confounding, it was determined that there was no confounder. Backward selection procedure was done to determine which variables will be included in the final model. The interacting variables age by palliative care, and resective surgery by histology were not significant and thus were removed from the model. Sex, malignancy, and alcohol intake status were also removed from the model but in the final model, sex was later retained since it is a known confounder. Comparing the two resulting model, the backward strategy and the one with forced variables using the Bayesian Information Criterion, the model with forced variables was chosen as the final model since it has lower BIC (BIC=8647.794) than the full model (BIC=8757.32).

Table 4 shows the variables that were included in the final generalized-gamma model. The p-values were compared at 5% level of significance. In categorical variables, time ratio was defined as the proportion of survival time between the categories of the variable and the reference category. In continuous variables, time ratio indicates whether the survival time of a particular event increases, decreases or remains constant.[13]

Table 4. *Risk factors for lung cancer survival.*

Risk factors	Time Ratio	Standard Error	z	P-value	Over-all P-values	95% Confidence Interval
Age per admission	1.03	0.02	1.58	0.1140	0.0000	[0.9931, 1.0664]
Age per admission*Age per admission	1.00	0.00	-0.94	0.3470		[0.9996, 1.0002]
Sex (0=Female, 1=Male)	0.76	0.09	-2.20	0.0280	0.0280	[0.5983, 0.9711]
Residence (0=Other regions, 1=NCR)	0.89	0.05	-2.14	0.0320	0.0320	[0.7964, 0.9899]
Smoking status (0=Non-smoker, 1=Smoker)	0.74	0.06	-3.60	0.0000	0.0000	[0.6271, 0.8715]
Pneumonia (0=No, 1=Yes)	0.73	0.07	-3.28	0.0010	0.0010	[0.6082, 0.8823]
PTB (0=No, 1=Yes)	0.99	0.06	-0.23	0.8200	0.8200	[0.8666, 1.1200]
COPD (0=No, 1=Yes)	0.74	0.08	-2.79	0.0050	0.0050	[0.5957, 0.9134]
Presence of metastasis (0=No, 1=Yes)	0.69	0.08	-3.01	0.0030	0.0030	[0.5482, 0.8804]
Number of admissions	1.17	0.02	9.71	0.0000	0.0000	[1.1325, 1.2061]
Previous surgery elsewhere (0=No, 1=Yes)	0.71	0.10	-2.48	0.0130	0.0130	[0.5429, 0.9306]
Previous chemotherapy elsewhere (0=No, 1=Yes)	0.97	0.21	-0.14	0.8870	0.8870	[0.6317, 1.4874]
Previous radiotherapy elsewhere (0=No, 1=Yes)	0.62	0.14	-2.10	0.0350	0.0350	[0.3961, 0.9676]
Previous other treatment elsewhere (0=No, 1=Yes)	1.06	0.13	0.48	0.6340	0.6340	[0.8312, 1.3547]

NSCLC: Squamous	0.74	0.14	−1.55	0.1220		[0.5101, 1.0826]
NSCLC: Adenocarcinoma	0.94	0.11	−0.54	0.5880	0.2772	[0.7481, 1.1787]
NSCLC: Others	1.68	0.83	1.05	0.2940		[0.6381, 4.4164]
Stage IIA and IIB	0.76	0.15	−1.37	0.1700		[0.5056, 1.1279]
Stage IIIA	0.64	0.11	−2.61	0.0090		[0.4615, 0.8961]
Stage IIIB	0.33	0.06	−6.02	0.0000	0.0000	[0.2313, 0.4746]
Stage IVA	0.47	0.09	−4.08	0.0000		[0.3296, 0.6770]
Stage IVB	0.36	0.07	−5.62	0.0000		[0.2525, 0.5146]
Diagnostic procedure at LCP (0=No, 1=Yes)	1.26	0.09	3.08	0.0020	0.0020	[1.0863, 1.4525]
Supportive care at LCP (0=No, 1=Yes)	0.95	0.35	−0.14	0.8860	0.8860	[0.4588, 1.9599]
Palliative care at LCP (0=No, 1=Yes)	1.37	0.90	0.48	0.6330	0.6330	[0.3783, 4.9464]
Chemotherapy at LCP (0=No, 1=Yes)	29.69	7.67	13.12	0.0000	0.0000	[17.8884, 49.2709]
Surgery at LCP (0=No, 1=Yes)	1.90	0.67	1.83	0.0680	0.0680	[0.9542, 3.7995]
Radiotherapy at LCP (0=No, 1=Yes)	2.19	0.33	5.14	0.0000	0.0000	[1.6230, 2.9502]
COPD x PTB	1.49	0.24	2.44	0.0150	0.0150	[1.0812, 2.0501]
Stage IIA and IIB with supportive care	0.53	0.28	−1.20	0.2280		[0.1851, 1.4956]
Stage IIIA with supportive care	1.15	0.50	0.33	0.7430		[0.4941, 2.6873]
Stage IIIB with supportive care	0.87	0.39	−0.32	0.7520	0.0288	[0.3583, 2.0998]
Stage IVA with supportive care	0.57	0.22	−1.46	0.1440		[0.2722, 1.2082]
Stage IVB with supportive care	0.58	0.23	−1.40	0.1600		[0.2697, 1.2418]
Stage IIA and IIB with palliative care	2.87	2.67	1.14	0.2560		[0.4645, 17.7729]
Stage IIIA with palliative care	2.56	2.04	1.18	0.2400		[0.5347, 12.2322]
Stage IIIB with palliative care	2.39	2.07	1.01	0.3130	0.0035	[0.4389, 13.0615]
Stage IVA with palliative care	0.88	0.58	−0.19	0.8480		[0.2414, 3.2166]
Stage IVB with palliative care	0.65	0.43	−0.65	0.5150		[0.1750, 2.3965]

Male with squamous cell carcinoma	1.78	0.37	2.75	0.0060	0.0055	[1.1794, 2.6856]
Male with adenocarcinoma	1.41	0.19	2.49	0.0130		[1.0763, 1.8476]
Male with other NSCLC	0.51	0.28	–1.23	0.2210		[0.1698, 1.5055]
Constant	77.07	42.90	7.80	0.0000	0.0000	[25.8830, 229.4630]

A time ratio greater than 1 or significantly higher survival were seen with diagnostic procedure at LCP, number of admissions, radiotherapy at LCP, and chemotherapy at LCP. On the other hand, time ratios that are less than 1 such as seen with region of origin (NCR), males, smokers, presence of pneumonia and COPD, presence of metastasis, previous surgery elsewhere, and previous radiotherapy elsewhere showed significantly lower survival.

Table 5 demonstrates that there was high number of deaths during the first month up to 3 years while the survival probability decreased through time.

Table 5. *Life table of lung cancer patients at different time intervals.*

Time Interval	Number of subjects at the beginning	Number of deaths	Lost	Survival Probability	Standard Error	[95% Confidence Interval]
0–31 days (0–1 month)	9117	860	733	0.9017	0.0032	[0.8953, 0.9078]
31–90 days (1–3 months)	7524	1356	241	0.7366	0.0048	[0.7270, 0.7459]
90–180 days (3–6 months)	5927	1242	324	0.5779	0.0055	[0.5670, 0.5886]
180–365 days (6mos–1 yr)	4361	1639	340	0.3519	0.0055	[0.3411, 0.3627]
365–1095 days (1–3 years)	2382	1778	164	0.0799	0.0033	[0.0735, 0.0865]
1095–1825 days (3–5 years)	440	257	37	0.0312	0.0023	[0.0269, 0.0359]
1825–3650 days (5–10 years)	146	120	22	0.0035	0.0009	[0.0021, 0.0056]
3650 days–onwards (10 years onwards)	4	4	0	0.0000	.	.

With regards to treatment, the patients with stage IA and IB disease and those who underwent chemotherapy showed the highest survival probability (Figures 1–2, appendices F–G) and worst among untreated patients.

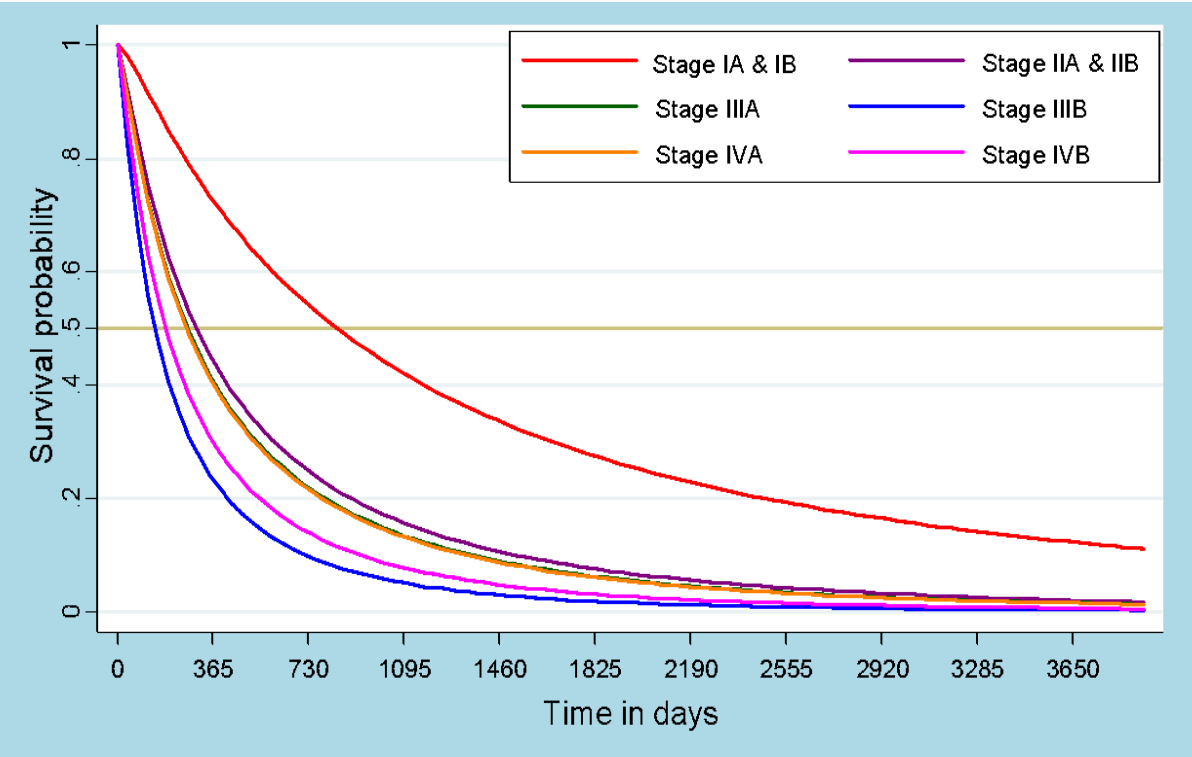

Figure 1. *Survival probability of lung cancer patients according to stage.*

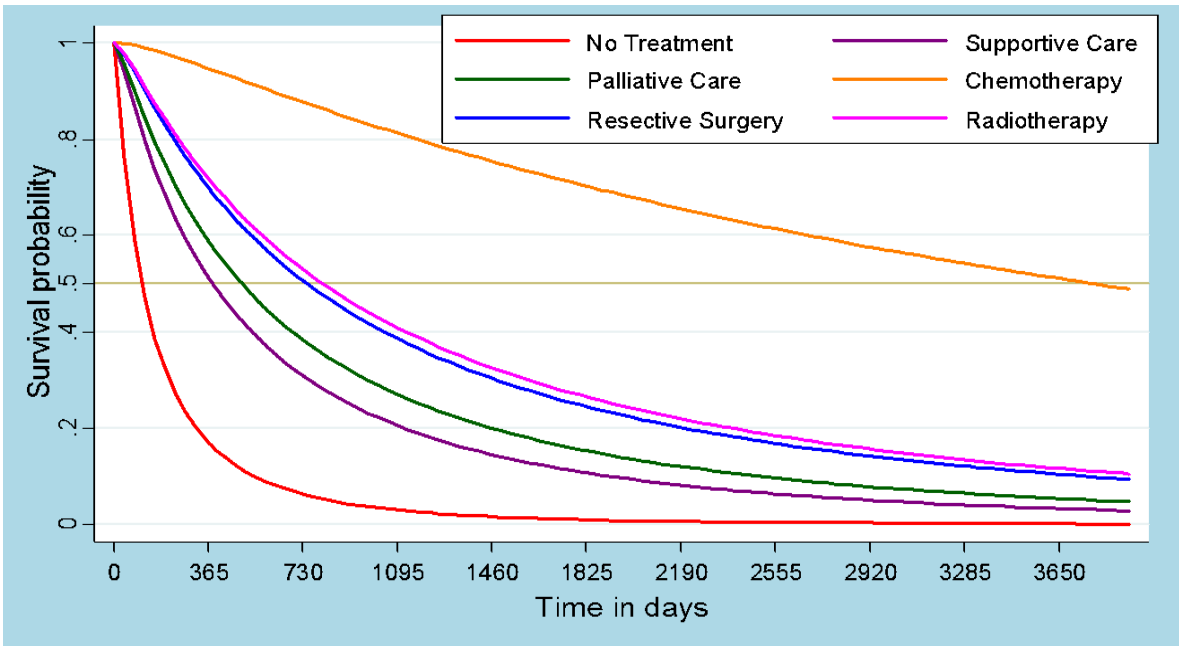

Figure 2. *Survival probability of lung cancer patients according to treatment.*

DISCUSSION

This study showed data for the period 2000 to 2009 from our institution's Lung Cancer Registry. The patient profile was consistent with existing literature, namely male–predominance (70.7%), and association with old age (54.3%) and smoking history (71.7%).

Females comprised 29.3% of cases in our cohort. While females still comprise a minority of lung cancer cases, the incidence is rising steadily. Several observations suggest that important sex-related distinctions in lung cancer exist. These include differences in histologic distribution, prevalence in never–smokers, frequency of activating EGFR mutations, likelihood of DNA adduct accumulation, and survival outcomes. The common profile of females is that of younger age, non–smoker and higher proportion of adenocarcinomas compared to their male counterparts.[14–15]

A notable finding also is that 26.5% of the cohort were non–smokers. The World Health Organization estimates that 25% of lung cancer worldwide occurs in never smokers.[16] However, lung cancer in never smokers' proportions may vary widely. The percentage is probably closer to 10–15% in Western countries. Gender variations also exist with more than 50% in women in Southeast Asia, and approximately 2–6% in men in Western series.[17–19]

Only 4.6% of the patients were below 40 years old, confirming that lung cancer is quite rare in persons below 40 years of age. Studies have shown that lung cancer in the young are more likely to be females, with adenocarcinoma, non–smokers and with less co–morbidities compared to their older more counterparts.[20,21] However, young adults have no significant differences with the elderly in terms of clinical presentation, histology type, operability or stage of the disease, and proportion of genomic picture or actionable mutations.[22,23]

Galvez–Niño et al. showed a median survival time of 8.2 months in lung cancer patients 40 years or younger, with a range of 3 to 86 months.[20] Among lung cancer in 18–35 years old, Liu et al. showed a one–year over–all survival rate of 62.3%, and a three–year and five–year survival rate of 53.1%.[21] The poor prognostic factors were male sex, squamous cell type, stage IV and negative or unknown gene mutation status.[22]

It is also important to note 30% of cohort had a history of TB. There is evidence to suggest that tuberculosis (TB) may increase the risk of lung cancer through substantial and prolonged pulmonary inflammation, leading to host tissue damage, fibrosis, scar formation, and genetic alterations.[23] A recent meta–analysis reported tuberculosis to be associated with a 1.7–fold elevation in the risk of lung cancer.[24] The main hypothesis is that Mycobacterium tuberculosis causes chronic inflammation and thus promotes lung cancer.[25] Epidemiologic studies have revealed that TB is associated with an increased risk of lung cancer, especially adenocarcinoma.[26] The presence of TB may actually influence the course and prognosis of lung cancer. Patients diagnosed with lung cancer and active TB for more than half a year have a significantly better prognosis than those diagnosed within half a year. ECOG Performance Status and surgery might possibly affect the outcomes of patients with co–existent active TB and lung cancer.[27]

Adenocarcinoma was the predominant cell–type (47.9%) in the cohort. Adenocarcinoma is now the main histologic type, accounting for almost half of all the cases.[28,29] However, a significant percentage (30%) of the patients had unspecified NSCLC. If the tumor cannot be classified based on light microscopy alone, special studies such as immune–histochemistry and/or mucin stains are recommended to classify the tumor further as treatment and prognosis depends on the histology. It has been recommended that the use of the term NSCLC not otherwise specified should be minimized.[29]

The mortality rate of the enrolled cohort at the time of study was 72.2%. The incidence rate of mortality was 38 deaths per 10,000 person days. The median survival is days or 4 months. Survival probability at 6–12 months is 35%; 1–3 years is 8% and 3–5 years is 3%. The low rates of survival were likely due to the fact that 67.5% were diagnosed as Stage IV and only 13.1% at the early stage (Stage 1 and 2).

Data from CONCORD–3 show that for lung cancer patients diagnosed during 2010–2014, 5–year survival rate was below 10% in Thailand, Brazil, Bulgaria and India and between 10–20% in most countries.30 Data from a hospital–based lung cancer registry in Thailand (2013–2017) had a case–fatality rate of 86.0 per 100 person years. Using Kaplan–Meier the median survival time is 0.46 years or 5.51 months. Overall survival is 31.2% in 1 year; 12.9% in 3 years; and 10.2% in 5 years.[9] Survival rates, however, are improving in some countries. In a population–based study in Sweden, the over–all survival one– two– and five–year survival estimates increased between 1995 to 2016 from 38% to 53%, 21% to 37% and 14% to 24%.7 This indicates that current efforts aimed at increasing survival can be successful.

In this cohort, male sex, smoking history, concomitant pneumonia or COPD, presence of metastasis and previous surgery or radiotherapy elsewhere were associated with worse survival. Any treatment modality, even just supportive or palliative care was better than no treatment at all. Receiving chemotherapy prolonged survival. As expected, the highest survival was seen in Stages I and II, worst with Stage IV, emphasizing the crucial role of early diagnosis and appropriate treatment in lung cancer. Comparable data are available among Asian countries. A study in Thailand showed that sex, stage of the disease and histology were associated with survival in LC. After adjusting for sex, TNM stage and histologic type, multivariate analysis of their cohort also identified chemotherapy as an independent predictor of improved survival (adjusted HR = 0.48, 95%

CI: 0.42 to 0.55; P < 0.001.9 In a tertiary cancer care center in Bangladesh, lower survival was associated with older age, presence of any co-morbidity, poorer performance status and radiotherapy only. The receipt of combined radiotherapy and chemotherapy was associated with higher survival (HR=0.56, 95% CI 0.46, 0.65; p < 0.001).[10]

A major strength of the study is the large sample size–the largest cohort of reported cases of lung cancer in a single institution in the Philippines. As data were extracted from hospital records retrospectively, some information may have not been reported and maybe subject to recording bias. The study's single institution design limits its generalizability to other areas in the Philippines. The patients seen at the outpatient department were also excluded, which may be included in future research. Data on the molecular profile and the specific systemic treatment received may also be included in further research. Multi-center studies may also be conducted in the future.

CONCLUSION

This cohort of lung cancer cases from 2000 to 2009 had low a survival rate, with a median survival of only four months, likely due to the majority having the diagnosis made at the advanced stage of the disease. Based on the survival probability curves, chemotherapy and diagnosis at an early stage yielded the best probability of survival.

AUTHORSHIP

All authors have certified fulfillment of Scientific Proceedings authorship criteria.

DISCLOSURE OF CONFLICTS OF INTEREST

All authors have declared that they have no conflicts of interest.

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