ASSOCIATION OF COMORBIDITIES WITH THE SURVIVAL OF NON SMALL CELL LUNG CANCER

Submitted by

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DECLARATION

I hereby declare that this thesis, entitled **"Association of comorbidities with survival of Non Small Cell Lung Cancer"** is based on my work and it contains no material previously published or written by another person and not accepted for the award of any other degree of a university or other institute of higher education.

This research work was carried out in the Department of Oncology, Ahsania Mission Cancer Hospital, Mirpur, Dhaka under the joint supervision of Professor Naiyyum Choudhury, Professor and coordinator Biotechnology and Microbiology programmes, department of Mathematics and Natural Science, BRAC University, Mohakhali, Dhaka and Professor Dr. Syed Md. Akram Hussain, Professor and Senior consultant of Oncology at Ahsania Mission Cancer Hospital, Mirpur, Dhaka.

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CERTIFICATE

This is to certify that Asma Aminul Haque has completed the thesis entitled **"Association of comorbidities with survival of Non Small Cell Lung Cancer"** as a partial fulfillment of the requirements for the degree of Master of Science in Biotechnology thesis part by the BRAC University Dhaka, Bangladesh. This study has been conducted in the Department of Oncology, Ahsania Mission Cancer Hospital, Mirpur, Dhaka under our joint supervision.

Her work is original and the work is up to our full satisfaction.

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ABBREVIATION

AdC	Adenocarcinoma
AH	Atypical Hyperplasia
CEA	Carcino Embryonic antigen
G-CSF	Granulocyte-Colony Stimulating Factor
ECOG	Eastern Co-operative Oncology Group
EGFR	Epidermal Growth Factor Receptor
F-NAC	Fine-needle Aspiration Cytology
Gy	Gray
LCC	Large-cell Carcinoma
NSCLC	Non-Small Cell Lung Cancer
SqCC	Squamous Cell Carcinoma
HTN	Hypertension
DM	Diabetes Melitus

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ABSTRACT

Lung cancer constitutes the major mortality in the world and incidence of the disease varies considerably among different ethnic population throughout the world. Palliative chemotherapy has been a choice in advance Non-Small Cell Lung Cancer NSCLC as it has a better result than best supportive care (BSC). The Primary objective of the present study was Co morbidity analysis in patients with lung cancer and the secondary objective was to see the impact of co morbidity on survival of lung cancer (NSCLC) patients. This was a retrospective observational study. This study was carried out in the Department of Oncology at Ahsania Mission Cancer Hospital, Mirpur, Dhaka. This study was carried out during the period from January 2013 to December 2013 for one year of enrollment with a follow up of 6 months up to June 2014 which makes total study period of 18 months. All patients with an age above 18 years of both sexes presented with histologically confirmed stage IIIA, IIIB & IV NSCLC (Non Small Cell Lung Cancer) were enrolled in the study. Patient's data were collected from the indoor and outdoor medical records of the AMCH hospital. After selection, patients were divided into comorbid and non comorbid group. Comorbidity was defined by any associated disease except for cancer. For the Kaplan Meier survival analysis patients were contacted over the phone to see the status (Dead or Alive) on the last day of the study (2014). Total number of patients in this study was 100 with median age of 60. The numbers of patients suffering from Squamous cell carcinoma is 53 patients whereas that for adenocarcinoma is 47 patients. 49 patients were at stage IIIA/IIIB and 51patients were at stage IV. In the comorbid arm 30% patient have hypertension (HTN) followed by diabetes mellitus (DM) 22% and 18% patient have both HTN and DM. Non Co morbid arm has median survival of 12.788 months (95% CI: 7.5 – 18.06) and Co Morbid has 8.0 months (95% CI: 6.81 – 9.18) and the difference is statistically Significant ($P < 0.05$). According to the stratified histology than there is a statistically superior survival in Non Co-Morbid Adenocarcinoma 10.42 months than Co – Morbid Adenocarcinoma 8.0 months with a P value of 0.05. In stage IIIA/IIIB non co-morbid patients have 15.45 months and co-morbid patients have 9.0 months of median survival with a non significant difference. Younger patients (below 60 group) have median survival of 7.25 and 8.0 months in Non co-morbid and co-morbid group respectively. But older Non comorbid patients (above 60 group) the survival time of 14.36 months was almost

twice than that of Co-morbid patients 7.02 months and the difference is statistically significant ($P<0.05$).

Patients with Diabetes Mellitus tend to live longer (Median OS 12.0 months 95% CI 2.3 - 21.6) than the patients with Hypertension (Median OS 7.4 months 95% CI 2.0 -12.78). This difference in survival is statistically significant ($P < 0.05$). We have observed that 68% of patients were alive less than a year. One year survival was observed in 27% of cases whereas two year survival was observed in 5% of overall population. Co-morbid patients had low survival months. Among 50 co-morbid patients 39 have survived less than a year, 9 patients have survived 1 year and only 2 have survived 2 year. A higher survival rate is observed in Non co-morbid patients. One year survival was observed in 18 patients and 2 year survival was observed in only 3 patients in Non co-morbid group. 29 Non co-morbid patients were found in the group of less than a year survival which indicates a lesser mortality rate than co-morbid patients. The study revealed that co morbidity is strongly associated with the survival of Non Small Cell Lung Cancer patient in Bangladesh. Even co morbid elderly people are in greater risk of mortality.

Introduction

Lung cancer ranks among the most common and most lethal malignancies worldwide. In the United States, 2006 cancer statistics showed that lung cancer was the second most common cancer for both men and women (92,700 or 13% of all cases, and 81,770 or 12% of all cases, respectively), but the number-one cancer killer in both sexes (90,330 men, 31% of all cancer-related deaths; and 72,1300 women, 26% of all cancer-related deaths) [1]. Lung cancer is rapidly emerging as a major cause of mortality in the Middle East, Africa, and Asia as well. The incidence of lung cancer varies considerably among different ethnic populations throughout the world. The global rise in lung cancer incidence, together with the fact that the overall 5-year survival of patients with this disease is less than 15%, underscores the magnitude of the lung cancer epidemic.

Carcinoma of lung was the most common cancer among the patients who attended National Institute of Cancer Research and Hospital (NICRH), Bangladesh. A total of 3,209 lung cancer patients attended during three years (2005-2007), 86% (2,763) of them were males. The number of lung cancer patients were increasing year by year; there were 902 lung cancer patients in 2005, 1,076 in 2006 and 1,231 in 2007 [2]. This again is the only data of the hospital and the real situation is probably worse than this. Lung cancer death rates for men khave dropped by 19% during the past decade, whereas these rates continued to increase in women up to the year 2002. Lung cancer was revealed as the leading cancer among males in the medical oncology department of NICRH [3].

1. Literature Review

1.1.Types of Lung Cancer

Lung cancer is divided into 2 main types, small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The category of the cancer determines the treatment options.

1.1.1. Small Cell Lung Cancer

Small **c**ell **l**ung **c**ancer (SCLC) accounts for about 15% of all lung cancers [4] Also known as *oat cell carcinoma* SCLC tends to be aggressive. The cancer often grows rapidly and spreads to other regions including lymph nodes, bones, brain, adrenal glands, and the liver. Risk of developing SCLC is highly associated with tobacco smoking. Less than 5% of patients diagnosed with the disease have never smoked.

1.1.2. Non-Small Cell Lung Cancer

Non-**s**mall **c**ell **l**ung **c**ancer (NSCLC) is divided into three categories, based on appearance and other characteristics of the cancerous cells:

- **Squamous cell carcinoma (SCC):** SCC accounts for approximately 25-30% of all lung cancer cases. SCC is highly associated with tobacco smoking and usually develops in the central region of the lungs.
- **Adenocarcinoma:** Adenocarcinomas account for approximately 40% of all lung cancer cases. This cancer type usually develops in the outer region of the lungs.
- **Large Cell Carcinoma (LCC):** LCC accounts for approximately 10-15% of all lung cancer cases. LCC is associated with rapid tumor growth and poor prognosis.

Other, less common types of lung cancers include carcinoid tumors, adenoid cystic carcinomas, hamartomas, lymphomas, and sarcomas.

1.2.Etiology of Lung Cancer

Smoking is the primary risk factor for the development of lung cancer, accounting for 90% cases in men and 70% cases in women [5, 6]. Lung carcinogenesis is known to occur from an accumulation of several genetic alterations, most commonly with p53 mutations and deletions on chromosomes 3p, 5q, 9p, 11p, and 17p. These alterations are more frequent in smokers than in nonsmokers [7].

Industrial agents found in the environment, such as asbestos, coal tar fumes, nickel, chromium, arsenic, nickel, diesel exhaus have been related to the development of lung cancer.

Most Non-small cell lung cancers (NSCLCs) are directly attributable to cigarette smoking. A variety of occupational and environmental exposures have been implicated in the pathogenesis of lung cancer. These include asbestos and silica fibers, organic compounds such as chloral methyl ether and Polycyclic Aromatic Hydrocarbon (PAH), diesel fumes and air pollution, metals such as chromium and nickel, arsenic, and ionizing radiation. Of particular interest in this regard are the effects of fruits and vegetables, as well as micronutrients such as retinols, carotenoids, vitamin C. Zinc, copper, and selenium intake appears to be associated with reduced lung cancer risk [8].

Adenocarcinoma surpassed squamous cell carcinoma as the most common subtype of lung cancer in both men and women in the mid-1980s. Adenocarcinoma has been more common in women since the 1950s and became the most common lung cancer diagnosis in men in 1990 [9]. Smoking low-tar filter cigarettes may increase the rate of adenocarcinoma because these cigarettes have a higher nitrate content, which has been shown to produce adenocarcinoma in laboratory animals [10–12]. Among the various histologic types of lung cancer, adenocarcinoma has the slowest doubling time and small cell carcinoma has the fastest [13]. Lung cancer may spread via hematogenous routes or locally within the lymphatics. In most cases, lymph node metastases seem to occur earlier than distant hematogenous spread.

Lung cancer occurs mainly in the elderly. Because of a demographic shift towards an older population and improved survival of patients with cardiovascular diseases, more elderly people are at risk of developing lung cancer. The proportion of patients aged 70 or older has increased from 26% in 1970 to 43% in 2000 **[14]**.With the rising mean age, more patients will be diagnosed with one or more other serious diseases at the time of lung cancer diagnosis (comorbidity) [15-18].

The clinical management of lung cancer is therefore becoming increasingly complex. Furthermore, these patients are often excluded from clinical trials. This means that little is known about the best way to treat elderly patients with comorbidity and about the outcome of treatment such as complications and survival.

Through the 1960s, the predominant type of non-small cell carcinoma was squamous cell carcinoma. Although the overall incidence of lung cancer has dramatically increased during the past 30 years, the relative incidence of squamous cell carcinoma has decreased, and adenocarcinoma has become the dominant cell type, a phenomenon that has been temporally associated with the changes in tobacco blends and the use of filters in cigarettes. Adenocarcinomas are most often located in the periphery of the lung radio graphically, and in the smaller airways histologically. Therefore, they are not readily amenable to detection by sputum or other types of cytology, at least in their early stages, but become apparent in the relatively translucent pulmonary periphery on computed tomography (CT) scan in earliest stages and then on chest x-ray.

An important distinction is made between SCLC and NSCLC since these treatments are different. The choice of treatment is based on histology, general condition and extent of disease. The management of lung cancer should be based on histo-pathological type. NSCLC represents one treatment group and SCLC another [4]. For non-small cell lung cancer (NSCLC) the choice is between radical surgery, radical or palliative radiotherapy. The primary curative treatment for NSCLC is surgery. In stage I and stage II a complete surgical resection is almost always possible [4].

NSCLC is one of the most chemo resistant solid lesions with a response rate of 15-25% for single agent usually of 3-5 months duration. However, when combining two or three of the most active drugs the response rate increases to 30-50%, mainly due to new more active and less toxic cytotoxic agents, such as Taxanes, Vinorelbine and Gemcitabine. Commonly used regimens in NSCLC are Cisplatin-Paclitaxel, Cisplatin-Gemcitabine, Carboplatinum-Gemcitabine, Cisplatin-Vinorelbine, Carboplatinum-Paclitaxel and Docetaxel-Cisplatin

1.3 Epidemiology

Smoking is the main, although not the only, etiologic factor of lung cancer. An estimated 5%-20% of lung cancers arise in association with exposure to respiratory carcinogens, including asbestos. Only an estimated 10% of heavy smokers develop lung cancer. An estimated 20% of lung cancers arise in non-smokers and only 20% of these can be attributed to passive smoking [61].

Notably, diet has been proposed to be one of these factors and the usual aspects (fruits and vegetables) have been proposed to have a protective effect against the development of lung cancer in both smokers and non-smokers. This effect has been linked to a protective effect against mutations by nutrients.

From 1973 to 1994, a much larger increase in the incidence of lung cancer was observed for women than for men. Whether this increase suggests a higher gender-related risk of cancer for women merely reflects changing smoking patterns remains controversial. The overall increase in incidence of adenocarcinoma that has occurred since the 1960s has been correlated with the introduction of filter tips in cigarettes.

Different histological types of lung cancer have different associations with cigarette smoking and this association is the highest for squamous cell carcinoma (SqCC) and small cell carcinoma (SCC). Human papillomavirus (HPV) infection is an etiologic factor in the rare cases of SqCC of the lung that arise in the setting of laryngeal papillomatosis. HPV, including high risk serotype, has been detected in approximately 20% of patients with lung cancers; whether it constitutes a cofactor in the development of such cancer outside the setting of laryngeal papillomatosis, however, is not clear.

1.4. Natural History

It is often difficult to determine the site of origin of lung cancer. Garland et al. studied 463 patients, 150 of whom had less advanced tumors that were suitable for determination of the site of origin: 58% of these tumors originated in the right lung and 42% in the left lung. Once established, tumors are likely to grow with a constant doubling time, at least during the early stages of their development. Among the various histologic types of lung cancer, adenocarcinoma has the slowest doubling time and small cell carcinoma has the fastest. Efforts to detect lung cancers in earlier stages through screening programs have been unsuccessful. Screening programs funded by the National Cancer Institute (NCI) in the 1970s failed to justify screening with serial chest x-rays and sputum cytology. These studies demonstrated that although many cancers could be diagnosed at earlier stages, no

improvement in overall survival was shown for screens at intervals less than 1 year. Thus, an annual chest x-ray remains the current recommendation for screening [62].

Imaging technologies have improved during the past two decades. With the deficiencies of the previously mentioned studies in mind, lung cancer screening was revisited by the Early Lung Cancer Detection Project, Henschke et al. reported a trial of 1,000 patients at high risk (age older than 60 years, at least 10 pack-years of cigarette smoking, and no prior cancers) for development of lung cancer who underwent baseline and annual repeat low-dose computed tomography (CT) and chest radiography [62].

Noncalcified nodules were detected in 27% of the patients. Malignant disease was detected in 2.7% by CT and in 0.7% by chest radiography. Of the 27 detected cancers, 26 were resectable. The NCI-sponsored National Lung Screening Trial is now conducting a randomized controlled trial to test whether low-dose CT scanning can reduce lung cancer mortality in asymptomatic individuals. Subjects are randomly selected to undergo screening with low-dose CT or chest x-ray. The National Lung Screening Trial will enroll 50,000 high-risk heavy smokers (and former heavy smokers who quit within 15 years before randomization), age 55 to 74 years. Participants will undergo an initial screening and two subsequent annual screenings and will be observed for a minimum of 4.5 years. Final analyses are expected in 2009 [62].

1.5. Risk Factors of lung cancer

1.5.1. Diet

Observations in the 1970s showed that lung cancer patients had low levels of vitamin A which prompted intense interest in the potential role of diet in modulating lung cancer risk. Subsequent studies suggested that by inhibiting DNA damage, anti-oxidant micronutrients might reduce lung cancer risk [60].

Data regarding fruit and vegetables consumption and lung cancer risk are somewhat contradictory. CS protective effect of fruit consumption has been suggested in some but not all studies. On the other hand majority of studies performed to date indicate that increased vegetable consumption diminishes lung cancer risk and particularly carrots and tomatoes

appear to have a protective effect. Specific vegetables which can reduce lung cancer risk have not been defined yet [60]. Overall, the data pertaining to the impact of vitamins and micronutrients and lung cancer risk are inconclusive.

1.5.2. Etiology

A variety of agents have been proven to be carcinogenic in humans [63]. Tobacco smoke is the dominant agent and represents a complex mixture of physical and chemical carcinogens. There is direct relationship between the amount of tobacco exposure and risk of developing lung cancer.

The type of cigarette seems to also influence the risk; i.e. a filter actually decreases the risk. Stopping smoking is associated with a gradual decrease in the risk, but a long period of time (more than 6 years) is necessary before an appreciable diminution of risk occurs. Interestingly, in Asians, the proportion of cases attributable to active smoking may not be a high. Asbestos exposure is associated with the development of mesothelioma and also bronchogenic carcinoma. The risk from asbestos is particularly more pronounced when combined with cigarette smoking.

Atmospheric pollution has been indicated as a causative agent because the higher the incidence of lung cancer in urban than rural areas. A more direct relationship has been shown in cases of pitchblende miners who are involved with radioactive ores. Metals, mostly nickel and silver, but also chromium, cadmium, beryllium, cobalt, selenium and steel have been proven to be carcinogenic in animals and are occupational hazards, particularly when combined with other factors. Chemical products such as chloromethyl ethers have been associated with the development of lung cancer, especially small cell lung cancer (SCLC).

1.5.3. Genetic Disposition

Whereas the vast majority of lung cancers are attributable to cigarette smoking, fewer than 20% of smokers develop this disease. Although observations suggest a genetic disposition to lung cancer, to date, the genes conferring susceptibility to this disease remain elusive. Tumor

suppressor gene abnormalities are more common in small cell lung cancer and dominant oncogene expression is more frequent in non-small cell lung cancer (NSCLC).

Approximately three fourths of lung cancer is non-small cell carcinoma, which include squamous cell carcinoma, adenocarcinoma and broncho-alveolar carcinoma. Small cell carcinoma is a distinct disease of neuro-ectodermal origin and clinically aggressive tumor biologic process.

Surgical resection is the preferred treatment for NSCLC in clinical stage I and II disease. If surgical margins yield positive findings, post-operative radiation therapy is considered to reduce the possibility of local failure. Mediastinal irradiation is commonly recommended for patients with completely resected stage II disease. Medically inoperable disease in patients with early stage NSCLC is treated with radiation therapy.

For patients with clinically evident N2 disease, induction chemotherapy followed by radiation therapy is a common treatment. Neo-adjuvant chemo-radiation therapy remains investigational. Sequential or con-current chemotherapy and radiation therapy has increased survival in patients with stage III NSCLC in comparison with patients treated with radiation therapy [60].

1.6. Early Detection

The major problem in the treatment of lung cancer has been that patient at the time of symptoms, and thus diagnosis, usually have had advanced stage disease. This has encouraged researchers to setup screening programs to detect the disease in more localized stages. Screening programs using chest radiographs and sputum cytology have been disappointing, since these tests were not able to decrease mortality from lung cancer [62].

1.7. Symptoms of Lung Cancer

A. Symptoms of lung Cancer related to local tumor growth

I. Due to central tumor growth

- Cough

- Wheeze or stridor
- Postobstructive pneumonia(fever productive cough)
- Dyspnea with obstructive pattern on testing
- Hemoptysis
- Poorly localized, dull pain

II. Due to peripheral tumor growth

- Pleuritis or chest pain
- Dyspnea with restrictive pattern on testing
- Pleural effusion
- Cough

B. Symptoms of lung cancer due to Regional Spread

I. Nerve entrapment Syndromes

- Hoarner's Syndrome (enopthalmos, meiosis, ptosis), cervical sympathetic nerves
- Diaphragmatic paralysis- phrenic nerve
- Hoarness- recurrent laryngeal nerve on the left
- Ulcer pain with vasomotor changes- 8^{th} cervical and 1^{st} thoracic nerve

II. Vascular involvement

- Venous distension and swelling of the face, neck, upper chest
- Superior vene cava
- Temponade, heart failure, arrhythmia- pericardial involvement

II. Direct Invasion

- Dysphagea- esophageal compression or invasion
- Dyspnea, stridor- due to tracheal involvement
- Dyspnea due to pleural effusion
- Broncho-esophageal fistula

C. Lung Cancer Symptoms due to metastatic disease

I. Central Nervous system- Brain

- Headache and change in pattern of chronic headache
- Unexplained nausea/ vomiting
- Blurred vision
- Diplopia
- Confusion or change in mentality
- Focal weakness
- Seizures- jacksonian or grand mal
- Ataxia

II. Central Nervous system- spinal cord

- Back pain localizing over the spine
- Rodicular back pain
- Ataxia
- Bowel or bladder dysfunction
- Paraparesis or paraplegia

- Sensory loss- parasthesia or loss of position or sense

III. Central Nervous System- leptomeninges

- Change in mental state
- Isolated cranial nerve dysfunction
- Non-dermatomal pain syndrome
- Headache
- Visceral disturbances
- Nausea/ vomiting
- Bowel or bladder dysfunction

IV. Bone

- Back pain
- Long bone pain
- Rib pain
- Pathological fractures

V. Liver

- Right upper quadrant fullness/ pain
- Early satiety
- Hectic fevers with no infections etiology

VI. Adrenal gland

- Flank pain
- Adrenal hypofunction (Addison's disease- rare)

VII. Other sites

- GI Tract- nausea/ vomiting; epigastric pain
- Skin- subcutaneous nodules; breast masses
- Choroid- blurred vision

D. Common Paraneoplastic Syndrome associate with lung cancer

I. Endocrine

- Hypocalcaemia (ectopic PTH)
- Cushing's Syndrome (ectopic ACTH)
- SIADH (ectopic anti-diuretic hormone)
- Carcinoid syndrome (ectopic serotonin)
- Gynecomastia (ectopic beta-HcG)

II. Neurologic

- Eaton-Lamber Syndrome
- Optic neuritis
- Subadequate cerebellum degeneration
- Progressive multifocal leuko-encaphalopathy
- Autonomic neuropathy

III. Musculoskeletal

- Polymyositis
- Clubbing
- Pulmonary hypertrophic osteoarthropathy

IV. Hematologic

- Anemia of chronic disease
- Leukemoid reactions
- Thrombocytosis
- Hypercoagulative state (Trousseau's Syndrome, Marantic endocarditis or DIC)

V. Cutaneous

- Dermatomyositis
- Hyperkeratosis
- Acanthosis negricans
- Hyperpigmentation

VI. Miscellaneous

- Nephrotic syndrome
- Anorexia/ cachexia
- Vasoactive intestinal peptide secretion with severe diarrhea

E. Common Clinical Presentation of lung cancer

- Asymptomatic pulmonary nodule
- Change in "smoker's cough"
- Non-purulent pneumonia in an adult
- Persistent upper respiratory infection

- Hemoptysis
- Hoarseness
- Signs and symptoms of metastatic disease
- Signs and symptoms of a paraneoplastic syndrome
- Carcinoma of unknown primary site

1.8. Diagnosis of Lung Cancer

Patients presenting with the above symptoms mentioned in Section 5.7.3 require a chest X-ray. A lateral view may be helpful, a computed tomography (CT) Scan of the chest and upper abdomen is recommended before bronchoscopy as peripheral tumors will not be reached by bronchoscopy and in these cases, a CT guided biopsy is required for histopathological diagnosis. Magnetic resonance imaging (MRI) can be used to determine if there are direct invasion structures contraindicating surgery but is not superior to CT in detecting mediastinal disease.

1.8.1 PET scanning

Positron Emission Tomography (PET scanning) is not currently widely used in the diagnosis and follows up of patient with lung cancer. PET scanning is a high resolution, whole body technique which can demonstrate the extent of tumor spread. It is also useful in differentiating between benign and malignant pulmonary nodules. PET Scan detects lymph node spread more accurately than even spiral CT Scan.

1.9. Comorbidity

Comorbidity is the occurrence of concomitant disease in addition to an index disease of interest or the simultaneous occurrence of multiple diseases in an individual.

Comorbidity has an inherent influence on each patient's initial treatment and the treatment effectiveness of patient care. Previous studies have demonstrated that less aggressive treatment is given to patients with breast cancer, prostate cancer, lymphoma, or lung cancer who have specific existing comorbidities [19-24]. Several diseases such as hypertension, ischemic heart disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus (DM) are considered to have a significant influence on the survival of cancer patients [20, 25-28].

In the case of lung cancer patients, pulmonary and cardiovascular function may have a significant impact on survival [20, 29-32]. Elderly patients with Stage I or II lung cancer are less likely to receive surgery than younger patients [31]. Patients with COPD, cardiovascular disease, or DM comorbidity also have a lower resection rate. Morbidity and mortality of non-small cell lung cancer (NSCLC) patients following resection are associated with poor pulmonary function or cardiovascular disease [20]. Older NSCLC patients have a higher prevalence of comorbid cardiovascular disease or COPD, which may cause additional morbidity and reduce their survival. NSCLC patients with comorbidity have a two-fold increased risk of death compared with patients without comorbidity [29].

The presence of multiple comorbid diseases is common among lung cancer patients, with 22.1% of patients having five or more comorbid diseases, 54.3% having three or more, and 88.3% having one or more [32-34]. Tuberculosis (TB), COPD, and DM are the most common comorbidities associated with a reduced survival among patients with lung cancer [32]. It was also identified that comorbidity is important for predicting the survival of both localized and advanced lung cancer [34].

The symptoms of lung cancer can be masked by the symptoms of comorbid diseases such as chronic bronchitis, COPD, TB, DM, hypertension (HT), or even heart disease [33,35,36]. Patients with comorbid diseases may ignore symptoms or delay reporting them to a physician, because the symptoms of lung cancer are often confused with those of comorbid diseases. Comorbid diseases may exert direct effects on the host immune system and reduce

the duration of survival, and are thus among the most important factors for determining lung cancer survival [37, 38].

Lung cancer is associated with age and smoking, and both age [39, 40] and smoking [41, 42] are strongly associated with comorbidity. Thus, it is expected that comorbidity has an important impact in lung cancer patients, yet to date comorbidity has not been well studied in this population. The common perception that most lung cancers are rapidly progressive and, as a consequence, almost all lung cancer patients die from their disease [43] may explain why the study of comorbidity in lung cancer patients has received restricted attention [59].

Co Morbidity
Diabetes Mellitus
Hypertension
Bronchial asthma
COPD
IDH
HTN & DM
COPD & HTN
DM & IDH

1.9.1 Lung cancer and COPD

COPD is a commonly encountered comorbidity in patients with lung cancer [44–46]. Indeed, recent studies have shown that COPD affects 50–90% of lung cancer patients [46, 47]. Moreover, patients with COPD are three to four times more likely to develop lung cancer compared with smokers with normal lung function [48, 49], and lung cancer is a major cause of mortality in COPD patients, particularly in those with mild or moderate disease [50]. However, it must be noted, that at least some of the association may be related to ‘detection bias’ in that subclinical COPD may be diagnosed during pre-assessment for lung surgery or radiotherapy in a lung cancer patient [51].

COPD has long been recognized as an indicator of a high risk of complications after lung resection [52, 53]. For example, in patients with lung cancer and COPD who undergo surgery,

postoperative pneumonia and tracheostomy are more frequent in patients with COPD than in those without [54]. Moreover, the presence of COPD significantly increases the risk of cardiac dysrhythmias, specifically supraventricular tachycardia [55]. Mortality rates are significantly higher in lung cancer patients who have postoperative pulmonary complications than in those who do not [52], and in comparison with lung cancer patients who do not have COPD, those with COPD have poorer long-term survival as a result of respiratory insufficiency [56], a higher rate of recurrence of the lung cancer [54], and poorer survival after surgery [57]. The clear link between the severity of the COPD and survival confirms COPD as a key prognostic factor in patients with lung cancer [57, 58].

1.10. Treatment (Management of Non-Small Cell Lung Cancer/ NSCLC)

The management of lung cancer should be based on the histopathological type. NSCLC represents one treatment group and SCLC represents another.

Surgery

Surgery offers the best chance of cure. Patients must be carefully selected as incomplete excision is of no benefit. Patients must undergo extensive staging and, in practice, only those with stage I and II tumors and good cardiopulmonary function are suitable for surgery.

Patients may have surgically resectable disease but are unable to tolerate a surgical procedure due to co-morbidity. These patients may be considered for radical radiotherapy.

In stage I and II NSCLC, a complete surgical resection is almost always possible. The procedure of choice is the one that encompasses all existing tumor tissues and provides maximum conservation of the lung tissue, as determined by the location and degree of tumor involvement including sampling of all mediastinal nodal stations or complete lymph node dissection. Segmented resection will be selected for patient with small, peripheral tumors (≤ 2cm in diameter), with no evidence of extension or metastases (T1N0M0). Lobectomy is performed for patients with centrally located tumor mass within the lobe and an adequate tumor free margin is required for this type of resection.

Pneumonectomy is the procedure of choice for patients having more extensive disease, with tumors extending to the orifice of the lobar bronchus and tumors originating within or extending to the main stem bronchus, with involvement of more than one lobe.

Radical Radiotherapy

Thoracic Radiotherapy

Thoracic radiotherapy is particularly challenging as the tumor is a moving target within as area surrounded by critical and radiosensitive tissues, such as lung parenchyma and spinal cord.

Palliative Radiotherapy

The volume of a treatment field is determined by the site of the tumor and diseaee extent but the dose for palliative treatment was established by a series of more trials published between 1991 and 1996. The effectiveness of palliative radiotherapy for the common symptoms control rates of lung cancer are hemoptysis 52%, cough 52% and pain 57% respectively. Bone pain and pathological features are common complications of lung cancer and can be controlled by a palliative dose of radiation. Brain metastasis with good performance status and controlled extracranial disease should receive whole brain radiotherapy.

Chemotherapy for Non-Small Cell Lung Cancer

The quality of life of patients with metastatic NSCLC may be improved by the judicious use platinum-based two drug combinations (doublets). A meta-analysis has shown a modest increase in survival of 1.5 months with platinum doublets compared to best supportive care.

Doublets of cisplatin with gemcitabine, paclitaxel, docetaxel or vinorelbine give similar response rates of 20.3% and a similar median survival of 8-10 months. The average 1 year survival is 30-30-40%. The addition of a third drug did not increase response rates or survival.

A meta-analysis showed cisplatin doublets produced a statistically significant better response rate and better survival when compared to carboplatin-based combinations. A combination of cisplatin (75mg/m^2) and the anti-folate drug pemetrexed (500mg/m^2) given 3 weekly is associated with fewer adverse side effects than other combination.

Combined Modality Therapy in Unresectable Stage III disease

As the effects of radiotherapy and chemotherapy used alone have been very modest, the combination of these has been explored extensively in non-resectable and locoregional NSCLC. The efficacy of concurrent chemoradiation has been confirmed in several meta-analysis of randomized trials, showing combined modality therapy to be superior to radiation alone, and it is now considered the standard of care for the treatment of locally advanced NSCLC.

What still remains to be classified are the optimal volume, dose, schedule and fractionation of radiotherapy, issues which are currently under investigation in multi-national trials, including identification of the best chemotherapy regimen.

Chemotherapy for Stage IIIb (malignant pleural effusion) and Stage IV disease

NSCLC is one of the most chemo-resistant solid tumors with a response rate of 15-20% for single agents, usually of 3-5 months durations. However, when combining two or three of the most active drugs, the response rate increase to 30-50%, mainly due to new more active and less toxic cytotoxic agents, such as taxanes, vinorelbine, and gemcitabine. No one regimen has been demonstrated to be superior in the first-line treatment for patients with advanced NSCLC.

At present, it is generally accepted that platinum-based chemotherapy should be the standard first-line treatment of advanced NSCLC patients in good performance status, since documented median survival benefit of 2-4 months is achieved and symptom relief is documented to occur in 40-60% of all patients. Chemotherapy is usually administered for no more than 4-6 cycles in patients with stage IV NSCLC.

Results and Prognosis

The overall survival rate for all patients treated is 5% - 10% with little impact made by current diagnostic screening procedures or newer multimodality approach in the common adenocarcinoma and SCC.

Overall Survival

According to SEER data, the relative 5 year survival rate is 8% to 10%, and the 10 year survival rate is 5% to 7%. For 5 years survivors, there is small rate of attrition; however 65% will still be alive at 10 years. The survival rate is somewhat better for female than for male-13% versus 10% at 5 years [60].

Biological Therapy

Much interest has focused on new biological agents against NSCLC including:

- Receptor-target therapy
- Signal transduction-cell cycle inhibitors
- Angiogenetic inhibitors
- Gene therapy
- Vaccines

Many of these agents are now in clinical development with most expensive having been obtained with the oral, small molecule EGFRtyrosine kinase inhibitors Gefitinib (Tressa TM)

and Erlotinib. Of these, Gefitinib has been extensively evaluated in both phase II and III trials. As a single agent, gefitinib resulted in response rate of 12-18% and symptom improvement is 40-43% lasting from a few weeks to several months at a dose level of 250mg or 500mg PO daily with inclusion of 103 and 102 NSCLC patients in the two trials. All patients had failed one or more previous chemotherapy regimens. Highest activity was observed among patients with adenocarcinoma, especially alveolar cell carcinoma and females. Very recent data indicate that clinical responsiveness to gefitinib is related to specific mutations in the EGFR gene.

2. Null Hypothesis

Co-morbidity (side diseases) are not associated with the survival of patients with Non Small Cell Lung Cancer.

3. Objectives

General Objective

- ✓ Analysis of Co morbidities in patients with lung cancer.

Specific Objective

- ✓ To assess the impact of co morbidities on survival of Non small cell lung cancer patients with standard treatment and care.

4. Research Methodology

Materials and Method

4.1 Types of Study

This was a retrospective observational study.

4.2 Place of study

This study was carried out in the Department of Oncology at Ahsania Mission Cancer Hospital, Mirpur, Dhaka.

4.3 Period of Study

This study was carried out during the period from **January 2013 to December 2013** for 1 (one) year for enrollment with a follow up of 6 months up to **June 2014** which makes total study period of 18 months.

4.4. Study Population

All patients with an age above 18 years of both sexes presented with histologically confirmed stage IIIA, IIIB & IV NSCLC (Non Small Cell Lung Cancer) were enrolled in the study.

4.5. Sample Size

A total of 100 patients were enrolled in the study and they were divided in to two arm. After 1:1 randomization both arm contains 50 patients and thus sample size was 100.Arm A contains non co morbid patients while arm B contains co morbid patients.

4.5.1. Sample Size Formula

Sample size was calculated using standard sample size formula which is

$$SS = \frac{Z^2 * (P) * (1-P)}{C^2}$$

Where:

Z = Z value

p = percentage picking a choice, expressed as decimal

c = confidence interval, expressed as decimal

Z value is always 1.96 for 95% Confidence level, p is 50% (0.5 when expressed as decimals)and c is the confidence interval and it is 8% i.e; margin of accepted error (0.08 in decimals).

So by putting value in the equation we get:

$$SS = \frac{(1.96)^2 * (0.5) * (1-0.5)}{(0.08)^2}$$

$$= \frac{3.8416 * 0.5 * 0.5}{0.0064}$$

$$= \frac{0.9604}{0.0064}$$

$$= 150.06$$

$$= 150$$

Our required sample size was 150.

4.5.2. Sampling Technique

Non Probability Quota sampling technique was applied for the study.

4.6. Selection criteria of subjects

4.6.1. Inclusion Criteria

- Unresectable or locally advanced histologically or cytologically confirmed NSCLC
- Male or female ≥ 18 years.
- At least one evaluable/measurable lesion with no symptomatic or history of untreated brain metastases
- Patients having at least one co morbidity such as diabetes mellitus, hypertension COPD etc.

4.6.2. Exclusion Criteria

- Patient aged less than 18.
- Patient with small cell or large cell carcinoma.
- Patient with no follow-up data.

4.7. Study design

In this single centered retrospective clinical study, previously recorded data were screened and checked for eligible patients. Data were collected only of those patients who were either co morbid or non comorbid with Non Small Cell Lung cancer.

4.8. Study Procedure

This was a retrospective observational study between two different group of lung cancer patient to compare the response and survival in patients with locally, advanced or metastatic NSCLC with Non co-morbidity or Co-morbidity.

Patient's data were collected from the indoor and outdoor medical records of the AMCH hospital. After selection, patients were divided into comorbid and non comorbid group. Comorbidity was defined by any associated disease except for cancer. For the Kaplan Meier survival analysis patients were contacted over the phone to see the status (Dead or Alive) on the last day of the study (2014).

4.8.1. Steps of the study procedure

Research Instrument

- A proforma for the questionnaire and recording of the clinical and laboratory findings.

4.8.2. Statistical analysis

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. All the statistical analysis was performed by using SPSS (

Statistical Package for Social Sciences) for windows version 20. 95% CI (Confidence Limit) was used, probability (*P)* value <0.05 was considered as a level of significance.

5. RESULT

5.1. Age distribution:

Total number of patients in this study was 100 with median 60 and range 57. Maximum frequency was 87 and minimum 30.

5.2. Age group:

Total number of patients was divided in three groups 20-39, 40-59, 60 and above. In age group 20-39 there were only 3 patients while in age group 40-59 there were 38 patients. Highest number of patients was in last group about 59 patients.

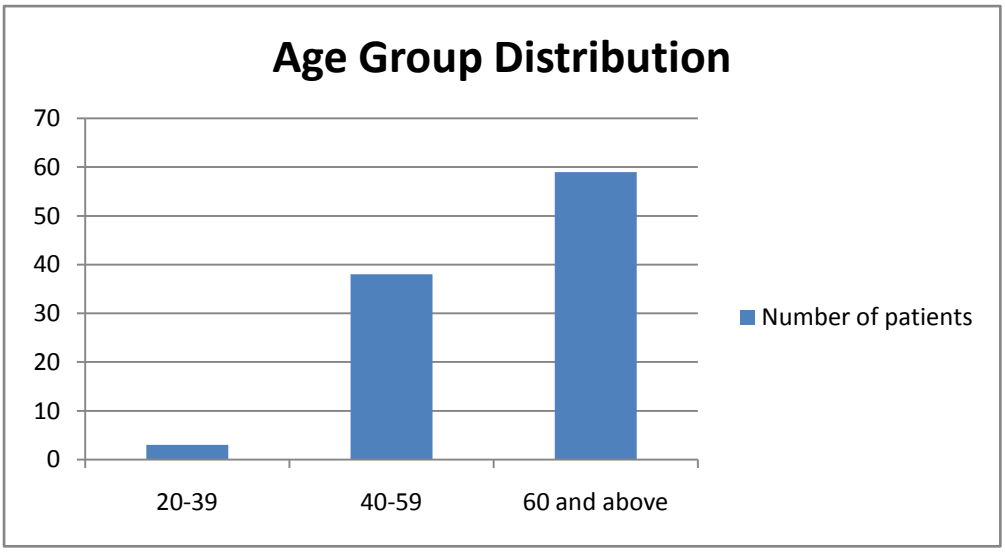

Fig. 1: Age group distribution

5.3. Sex:

It is seen that maximum number of patients are male about 85as compared to female 15. So males are more prone to lung cancer than female.

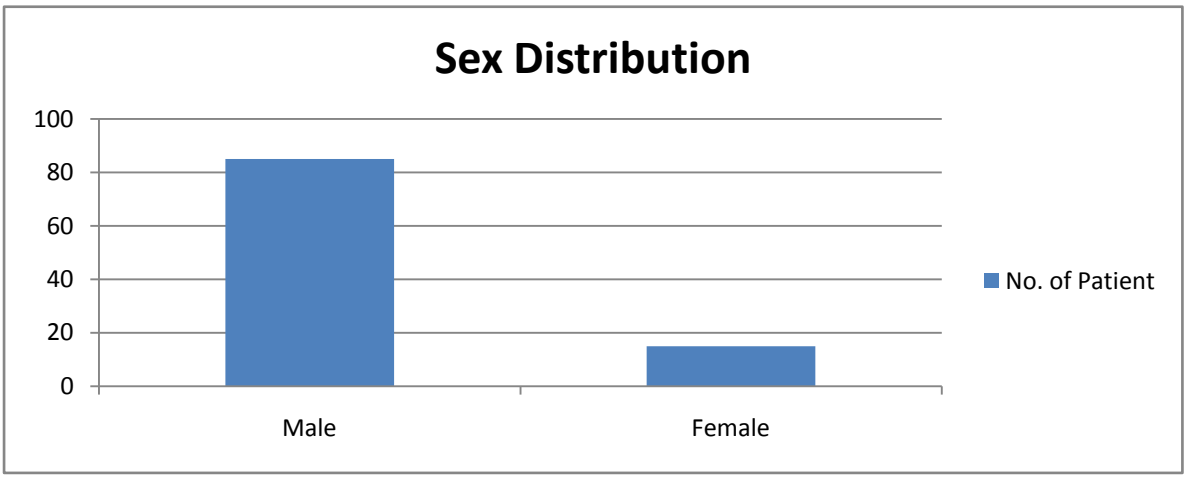

Fig. 2: Distribution according to sex

5.4. Histology:

According to histology the study was divided into two groups squamous cell carcinoma and adenocarcinoma.The number of patients suffering from Squamous cell carcinoma are 53 patients whereas adenocarcinoma includes 47 patients.

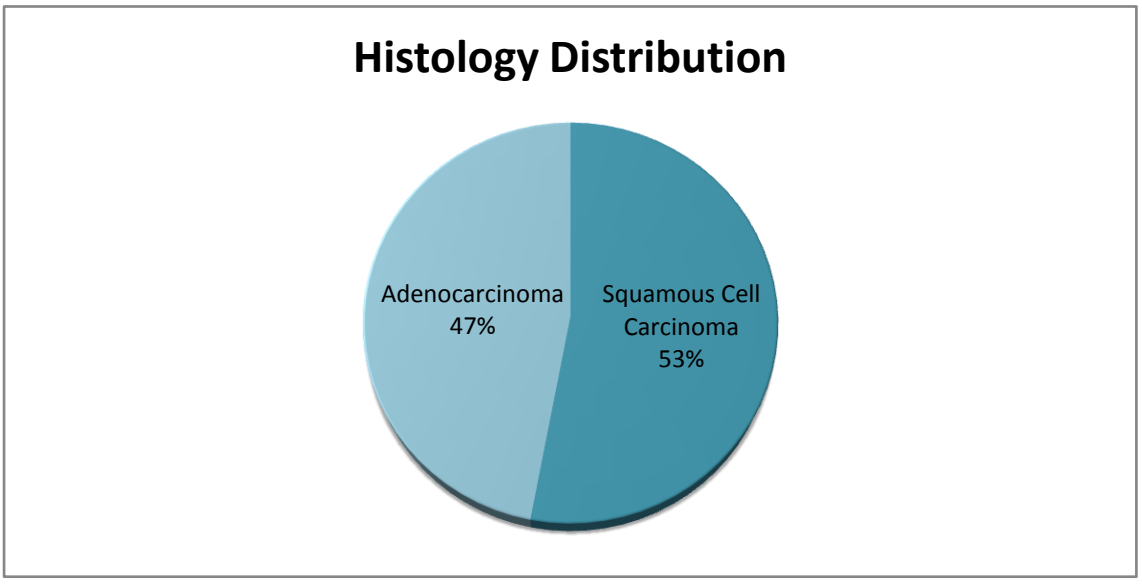

Fig. 3: Distribution according to Histology

5.5. Stages:

The study was divided in two stages IIIA/IIIB and IV.49 patients were at stage IIIA/IIIB and 51patients were at stage IV.

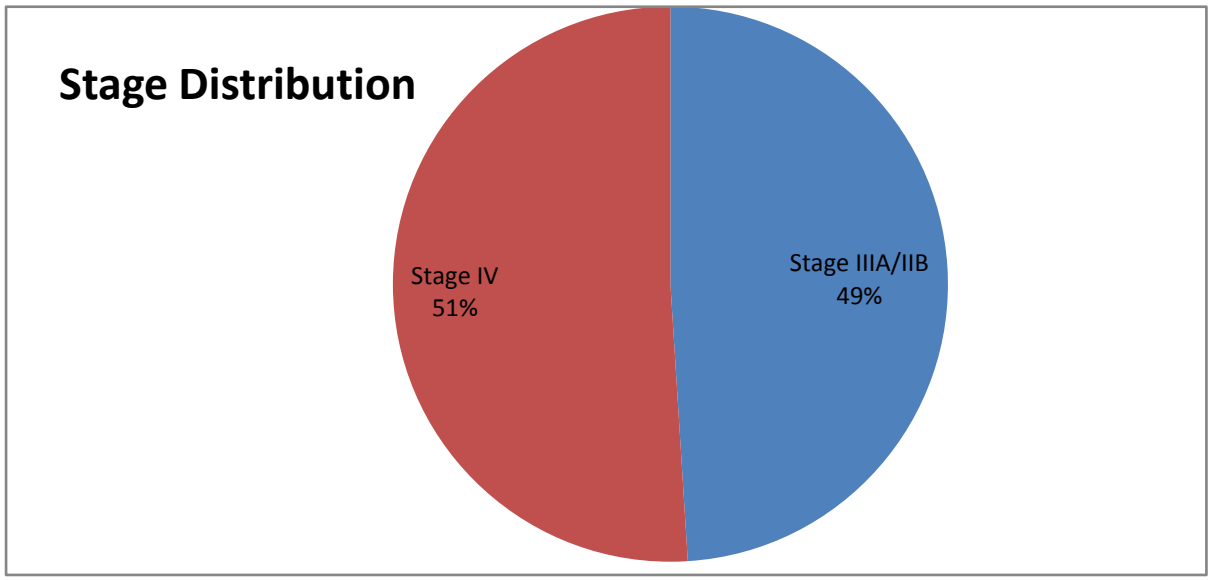

Fig. 4: Distribution according to Stage

5.6. Co morbidity

In the comorbid arm maximum (30%) patient were found to have hypertension (HTN) followed by diabetes mellitus (DM) (22%), 18% patient were found to have both HTN and DM.

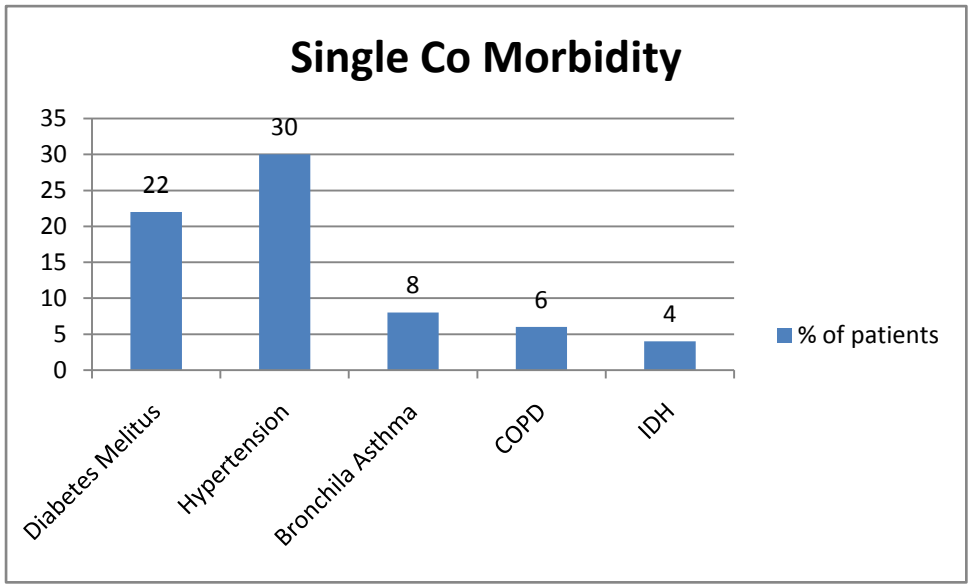

Fig. 5: Bar Charts showing distribution of patients with Single Co Morbidity

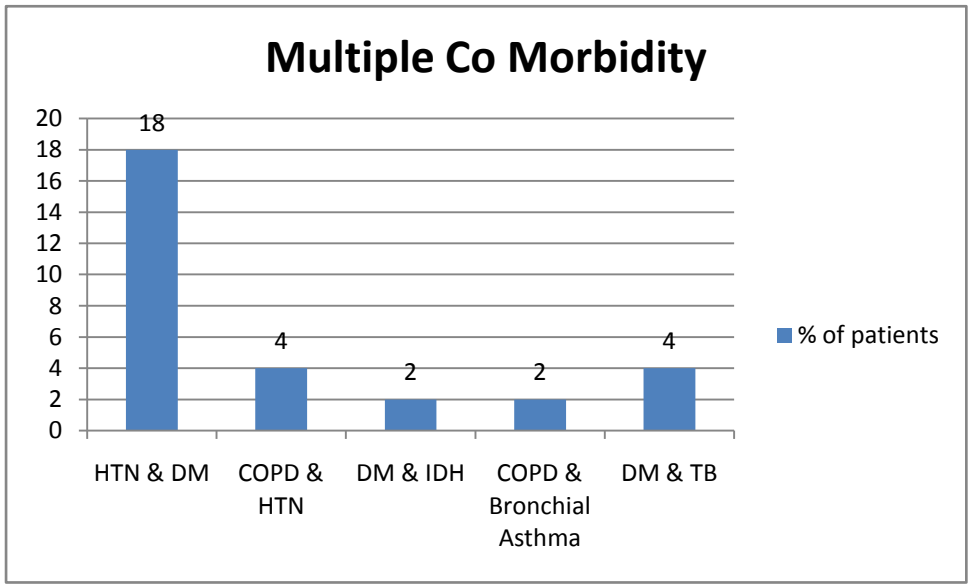

Fig. 6: Bar Charts showing distribution of patients with Multiple Co Morbidity

5.7. Patient Characteristics

Patient Characteristics is summarized in the table below.

Table 1: Characteristics of the study population.

Categories	Co-Morbid	Non Co-morbid
No. Of Patient	50	50
Median Age	64	60
Sex		
Male	43	42
Female	7	8
Histology		
Squamous Cell Carcinoma	27	26
Adenocarcinoma	23	24
Stage		
IIIA / IIIB	26	23
IV	24	27
Number of Co Morbidity		
One	32	N/A
Two	16	N/A
Three	1	N/A
Four	1	N/A

5.8. Survival Data

5.8.1. Overall Survival

Overall Survival was observed superior in non Co morbid arm than Co morbid arm. Non Co morbid arm has median survival of 12.788 months (95% CI: 7.5 – 18.06) and Co Morbid has 8.0 months (95% CI: 6.81 – 9.18) and the difference is statistically Significant ($P < 0.05$).

Table 2: Kaplan-Meier median overall survival data

Co-morbidity	Median			
	Survival in Months	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Non Co - Morbid	12.788	2.694	7.509	18.067
Co - Morbid	8.000	.603	6.819	9.181
Overall	**9.000**	**1.154**	**6.739**	**11.261**

Table 3: Log Rank (Mantel-Cox) test for significance for OS

Overall Comparisons			
Test	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.696	1	**.030**

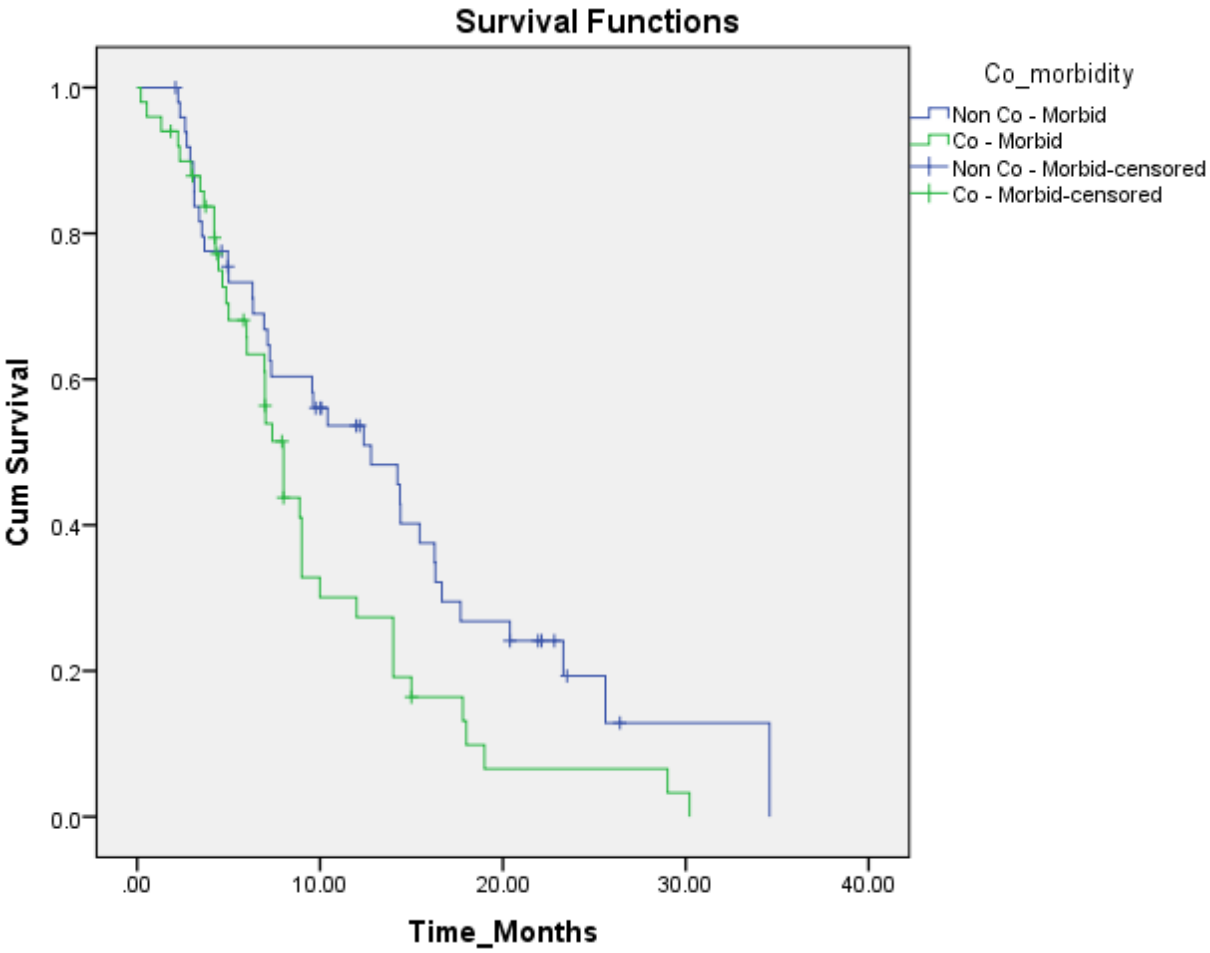

Fig. 7: Kaplan – Meier curve for overall survival

5.8.2. Survival According to Histology

If the data are stratified according to histology then there is a statistically superior survival in non Co-Morbid Adenocarcinoma (10.42, 95% CI: 1.07 – 19.76) than Co – Morbid Adenocarcinoma (8.0, 95% CI: 7.02 – 8.97) with a *P* value of 0.05.

In Squamous cell carcinoma non Co-morbid patients has median survival of 12.788 months (95% CI: 6.21 – 19.36) and Co-Morbid has 7.396 months (95% CI: 4.72 – 10.06).

Table 4: Kaplan-Meier median survival data (stratified by Histology)

Histology	Co - morbidity	Median			
		Survival in Months	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Squamous Cell Carcinoma	Non Co - Morbid	12.788	3.354	6.215	19.361
	Co - Morbid	7.396	1.362	4.726	10.066
	Overall	**9.632**	**2.847**	**4.051**	**15.213**
Adenocarcinoma	Non Co - Morbid	10.421	4.768	1.076	19.766
	Co - Morbid	8.000	.497	7.026	8.974
	Overall	**8.000**	**1.029**	**5.983**	**10.017**

Table 5: Log Rank (Mantel-Cox) test for significance on Histology interaction

Pair wise Comparisons						
Test	Histology	Co-morbidity	Non Co - Morbid		Co - Morbid	
			Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Squamous Cell Carcinoma	Non Co - Morbid			1.423	.233
		Co - Morbid	1.423	.233		
	Adenocarcinoma	Non Co - Morbid			3.855	**.050**
		Co - Morbid	3.855	**.050**		

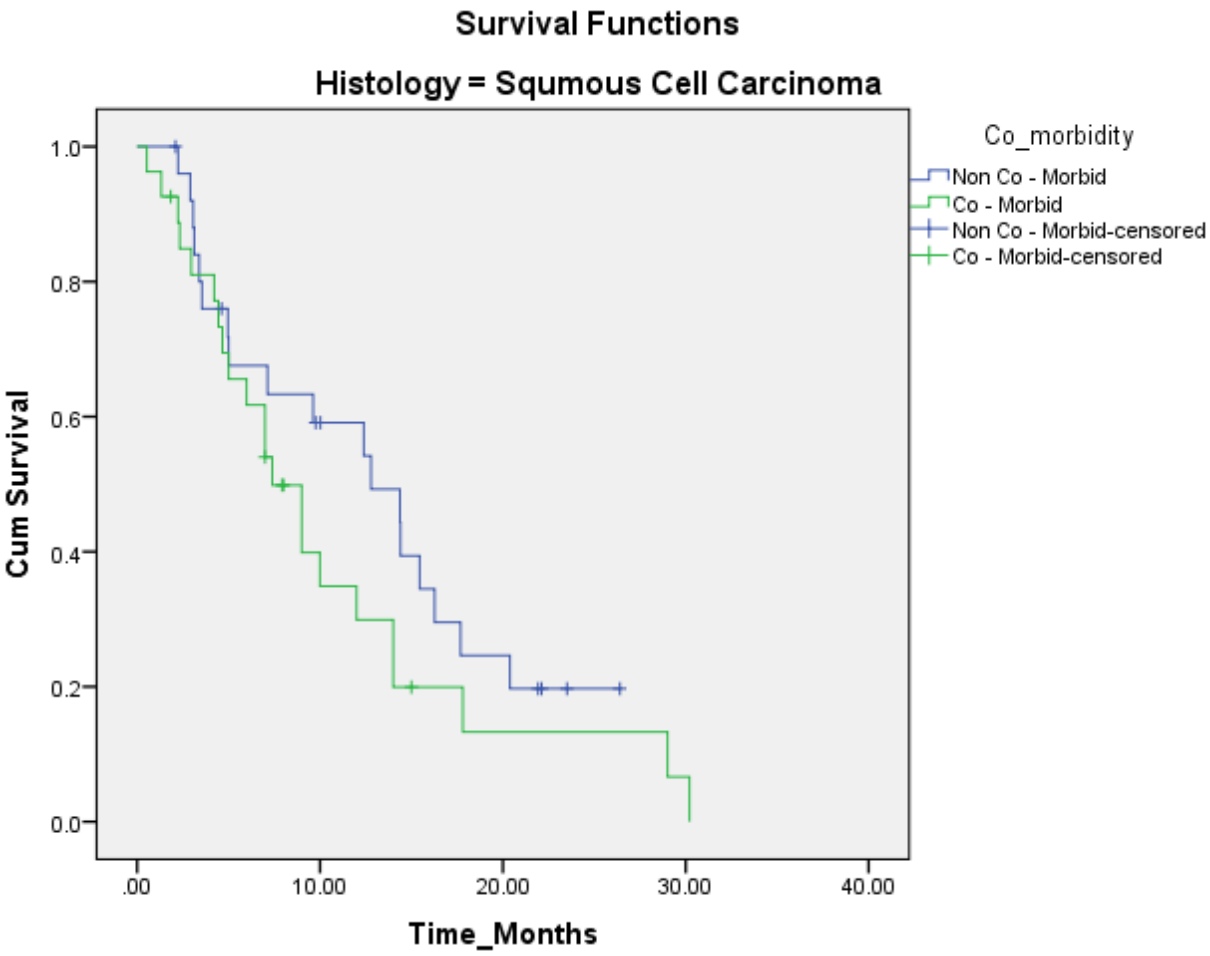

Fig. 8: Kaplan – Meier curve for Squamous cell carcinoma

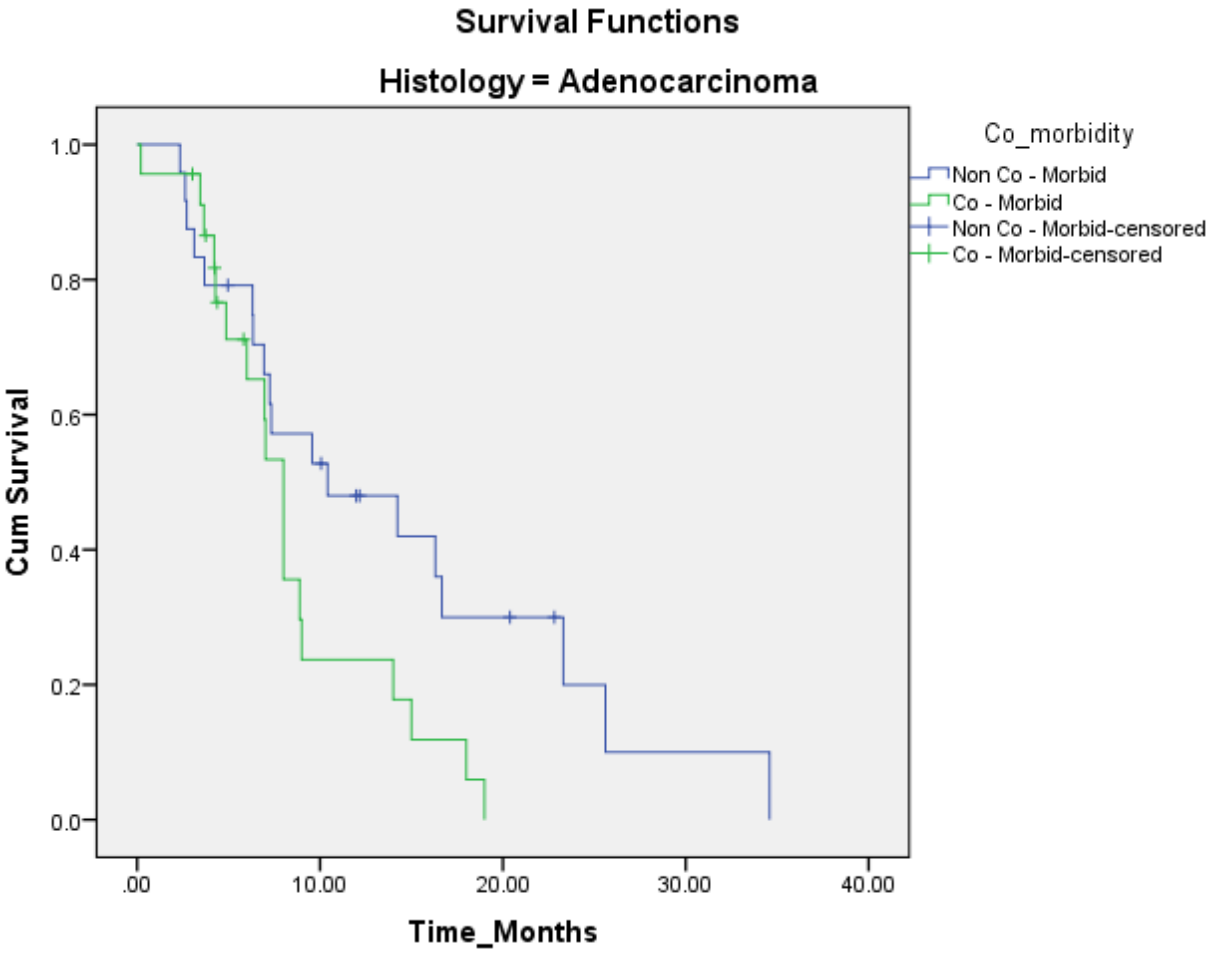

Fig. 9: Kaplan – Meier curve for Adenocarcinoma

5.8.3. Survival According to Stage

In stage IIIA/IIIB non co-morbid patients has 15.45 months and co-morbid has 9.0 months of median survival with a non significant *P* value of 0.12. Little lower results are observed in Stage IV, where non co-morbid has a survival of 9.6 months and co-morbid has 7.0 months.

Table 6: Kaplan-Meier median survival data stratified by Stage

Stage	Co-morbidity	Median			
		Survival in Months	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
III A / IIIB	Non Co - Morbid	15.450	2.864	9.837	21.063
	Co - Morbid	9.000	.659	7.708	10.292
	Overall	**10.000**	**2.192**	**5.704**	**14.296**
IV	Non Co - Morbid	9.632	2.354	5.017	14.247
	Co - Morbid	7.000	.770	5.491	8.509
	Overall	**8.000**	**1.030**	**5.981**	**10.019**

Table 7: Log Rank (Mantel-Cox) test for significance (stratified by stage)

Pair wise Comparisons						
	Stage	Co-morbidity	Non Co - Morbid		Co - Morbid	
			Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	III A / IIIB	Non Co - Morbid			2.380	.123
		Co - Morbid	2.380	.123		
	IV	Non Co - Morbid			3.114	.078
		Co - Morbid	3.114	.078		

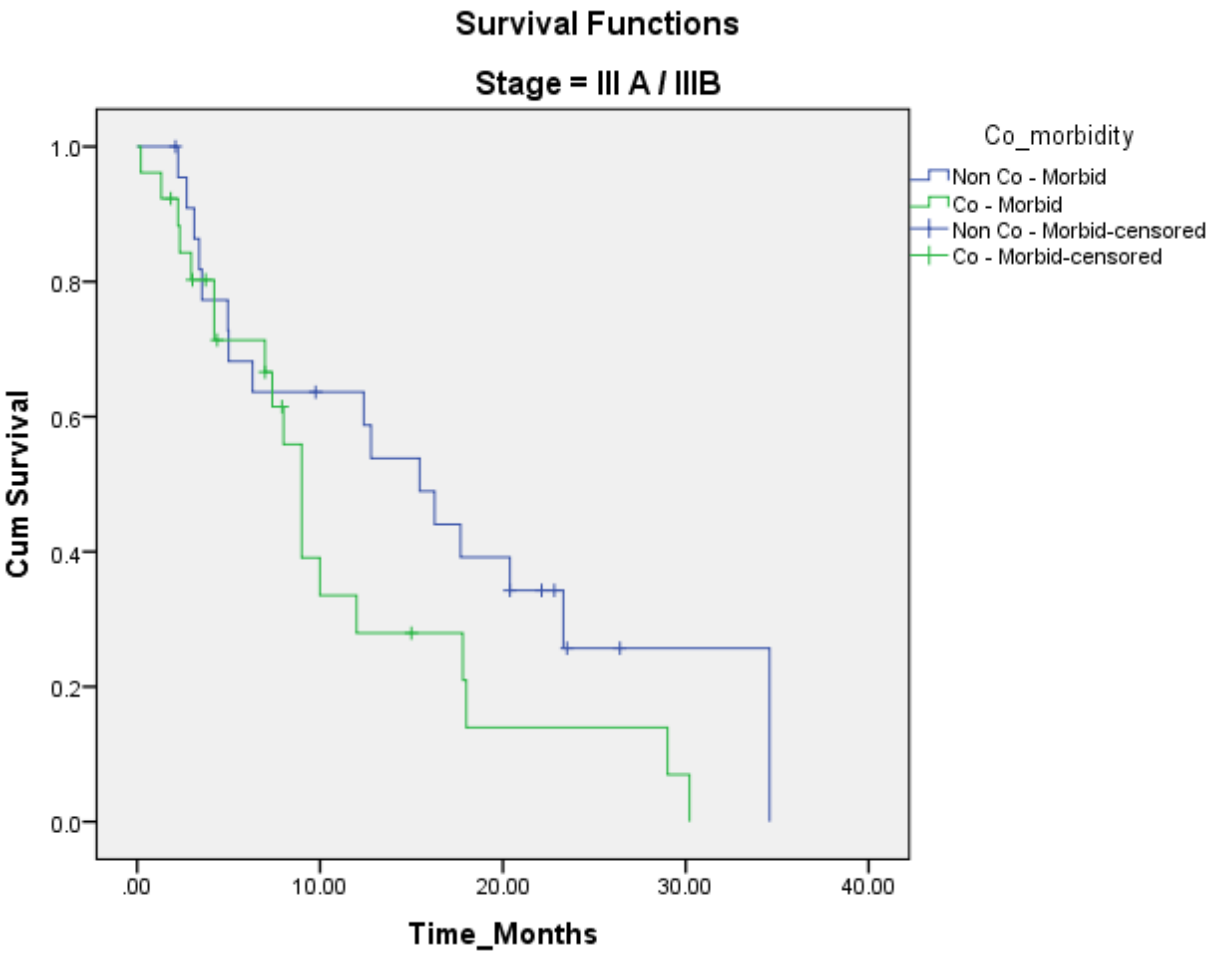

Fig. 10: Kaplan – Meier curve for Stage IIIA/IIIB

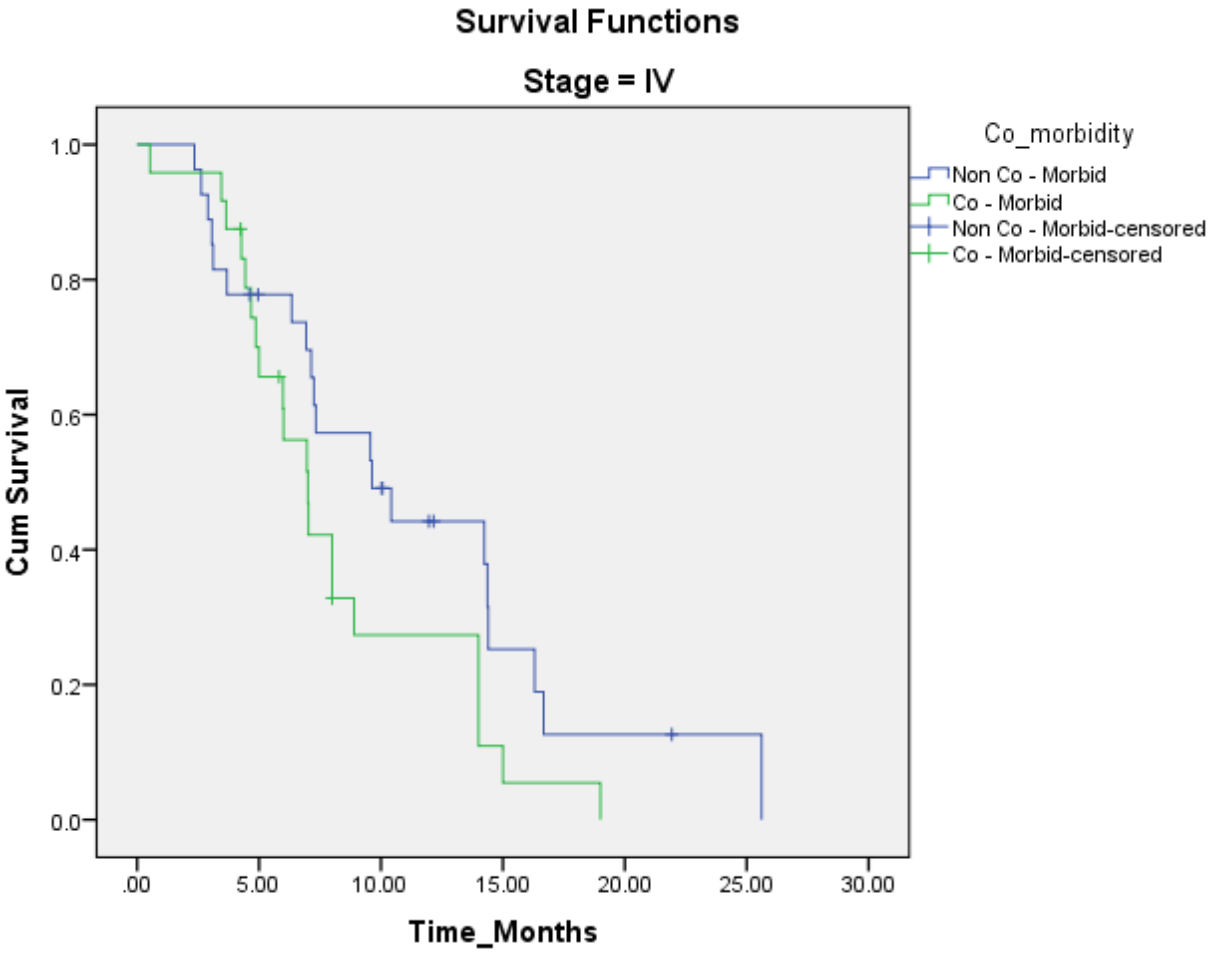

Fig. 11: Kaplan – Meier curve for Stage IV

5.8.4. Survival According to Age group

Younger patients (Below 60 group) have median survival of 7.25 and 8.0 months in non co-morbid and co-morbid group respectively. But older non co-morbid patients (Above 60 group) has almost twice the survival months (14.36) than Co-morbid patients (7.02) and the difference is statistically significant ($P<0.05$).

Table 8: Kaplan-Meier median survival data stratified by Age Group

Age group	Co-morbidity	Median			
		Survival in Months	Std. Error	95% Confidence Interval	
				Lower Bound	Upper Bound
Below 60	Non Co - Morbid	7.250	3.394	.597	13.903
	Co - Morbid	8.000	.677	6.673	9.327
	Overall	**8.000**	**.926**	**6.185**	**9.815**
Above 60	Non Co - Morbid	14.366	3.088	8.313	20.419
	Co - Morbid	7.021	1.212	4.646	9.396
	Overall	**9.632**	**1.767**	**6.169**	**13.095**

Table 9: Log Rank (Mantel-Cox) test for significance (stratified by age group)

Pair wise Comparisons						
Test	Age group	Co-morbidity	Non Co - Morbid		Co - Morbid	
			Chi-Square	Sig.	Chi-Square	Sig.
Log Rank (Mantel-Cox)	Below 60	Non Co - Morbid			.144	.704
		Co - Morbid	.144	.704		
	Above 60	Non Co - Morbid			5.117	**.024**
		Co - Morbid	5.117	**.024**		

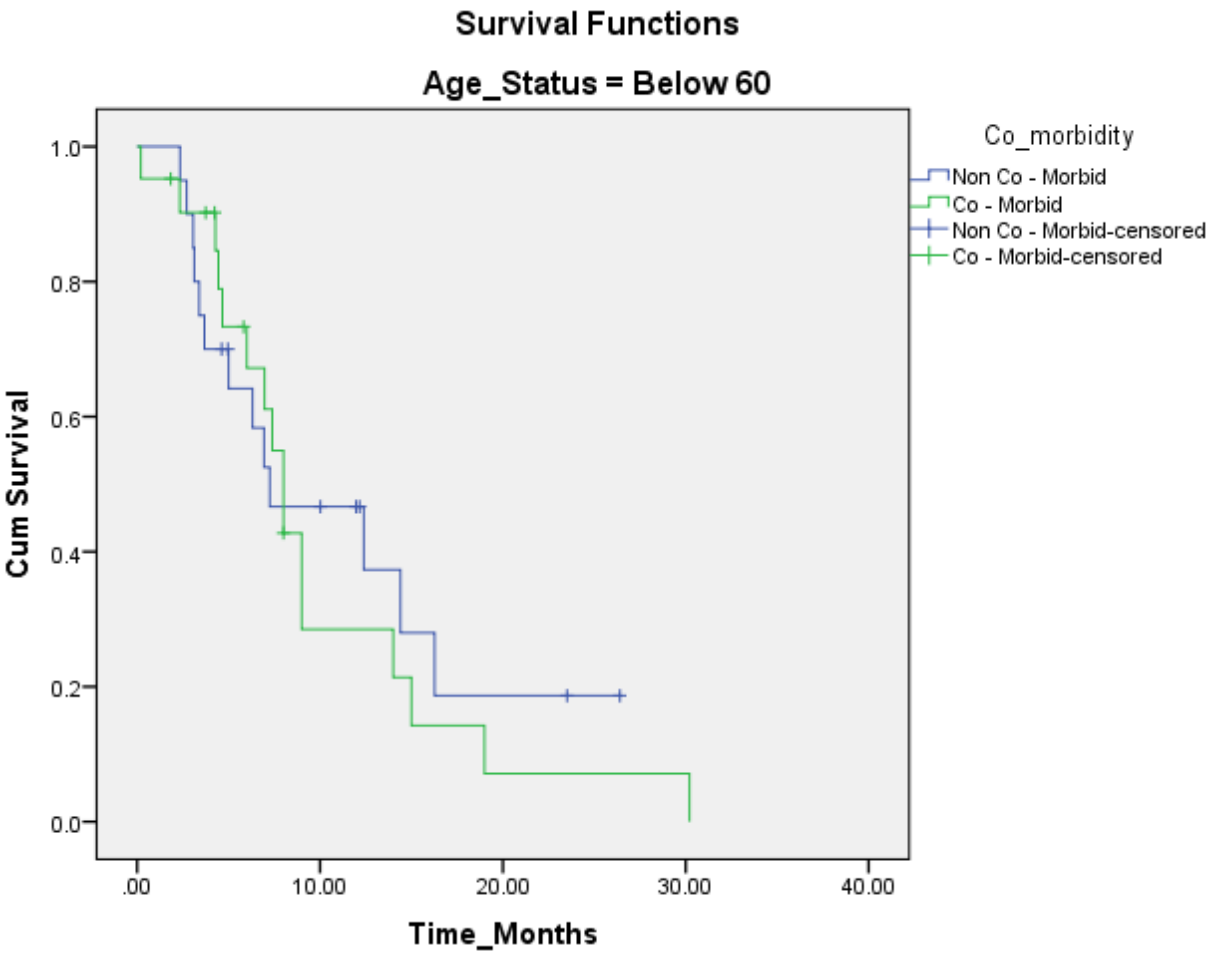

Fig. 12: Kaplan – Meier curve for Age below 60 group

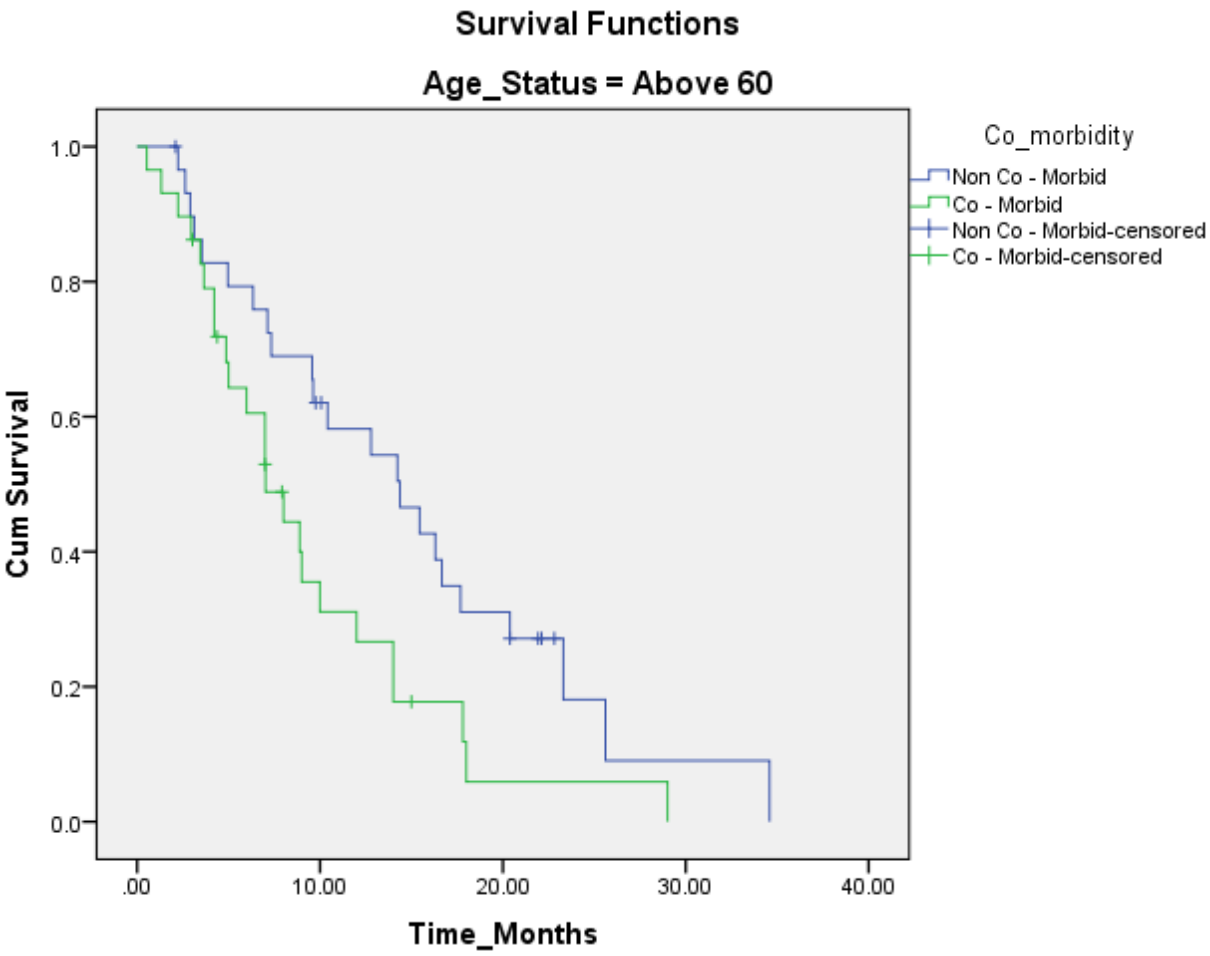

Fig. 13: Kaplan – Meier curve for Age Above 60 group

5.8.5. Survival according to the DM and HTN patient only

Patient with DM (Diabetes Mellitus) tends to live longer (Median OS 12.0 months 95% CI 2.3 -21.6) than with HTN (Hypertension) Median OS 7.4 months 95% CI 2.0 -12.78. This difference in survival is statistically significant ($P < 0.05$).

Table 10: Kaplan-Meier median survival data for DM and HTN patients only

Comorbidity DM , HTN	Median			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Diabetes Mellitus	12.000	4.947	2.304	21.696
Hypertension	7.396	2.748	2.009	12.783
Overall	9.000	1.118	6.808	11.192

Table 11: Log Rank (Mantel-Cox) test for significance (for DM and HTN only)

Overall Comparisons			
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	4.661	1	.031

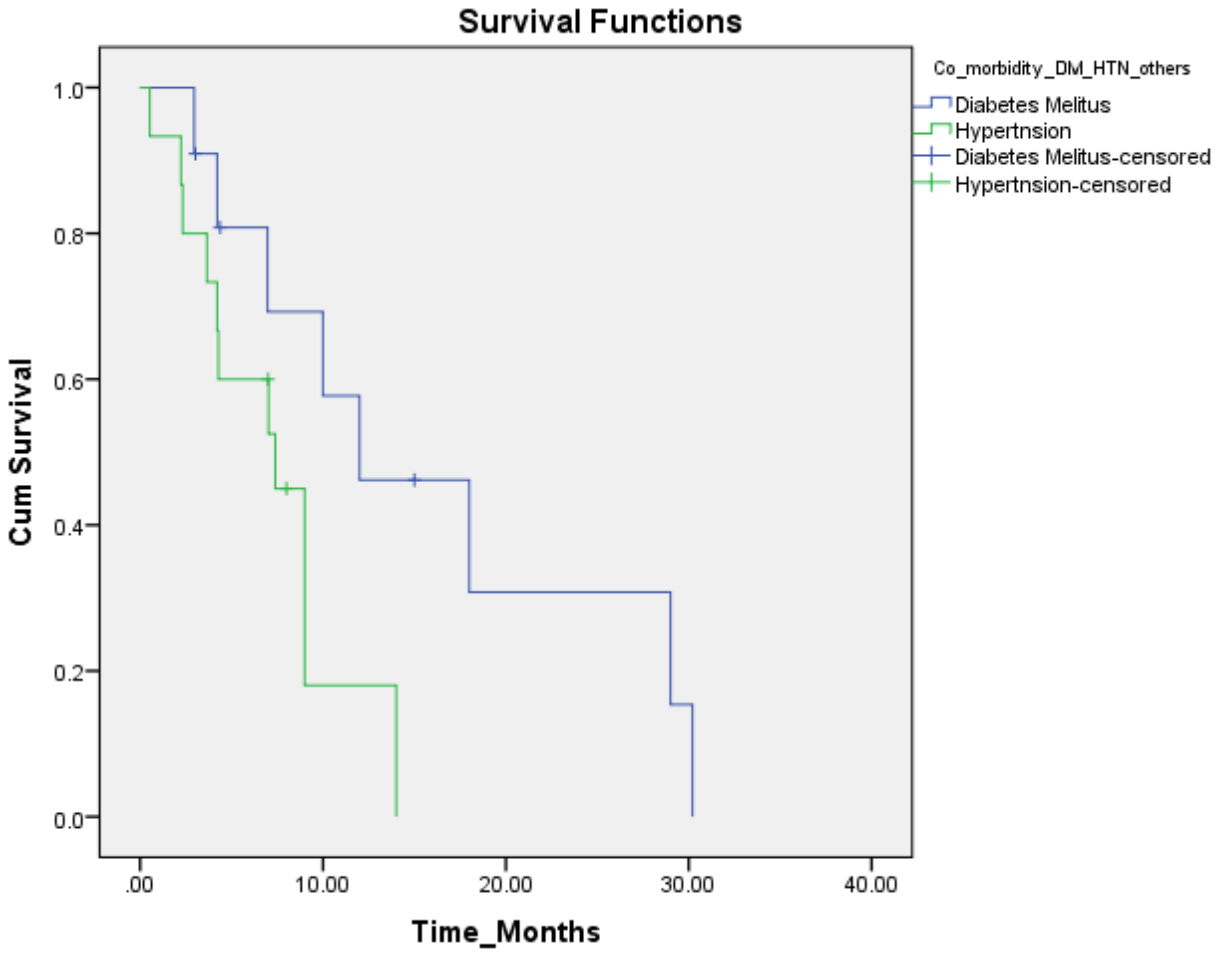

Fig. 14: Kaplan – Meier curve for DM and HTN patient only

5.9. Survival Rate

In our study we have observed 68% of patients have lived less than a year. One year survival was observed in only 27% of cases whereas two year survival was observed in only 5% of overall population.

Table 12: Survival Rate for the study population

		Overall Population	Percentage	Non Co-Morbid	Co-Morbid
Categories	Less than a year	68	68.0%	29 (58%)	39 (78%)
	1 year survival	27	27.0%	18 (36%)	9 (18%)
	2 year survival	5	5.0%	3 (6%)	2 (4%)
	Total	100	100.0%	50 (100%)	50 (100%)

By analysis of the survival data for non Co-morbid and Co-morbid patients, it is discovered that Co-morbid patients have low survival months. Among 50 patients 39 patients has survived less than a year, 9 patients has 1 year survival and only 2 patients were in 2 year survival group in Co-morbid patients. A higher survival rate is observed in Non co-morbid patients. One year survival was observed in 18 patients and 2 year survival was observed in only 3 patients in Non co-morbid group. 29 Non co-morbid patients were found in the group of less than a year survival which indicates a lesser mortality rate than co-morbid patients.

The whole survival analysis is summarized in the table 13

Table 13: Summarized Survival data for non co-morbid and co-morbid patients

Category		Non Co-morbid	Co-Morbid	*P* value
Survival In Months	Overall	12.79	8.0	**0.030***
	Histology			
	Squamous Cell Carcinoma	12.78	7.39	0.23
	Adenocarcinoma	10.42	8.00	**0.050***
	Stage			
	IIIA/IIIB	15.45	9.0	0.12
	IV	9.63	7.0	0.078
	Age group			
	Below 60	7.25	8.0	0.70
	Above 60	14.36	7.02	**0.024***
Survival rate (%)	**Survival rate (%)**			
	Less than a year survival	58%	78%	N/A
	One year survival	36%	18%	N/A
	Two year survival	6%	4%	N/A
Survival of Co-morbid patient only	**Co-morbidity**	**Median Survival**		***P* Value**
	DM	12.0		**0.031***
	HTN	7.39		

6. Discussion

In this retrospective study sample size was 100. The study was divided into two arm; Non Co-Morbid and Co-Morbid arm having 50 patients in each arm.

In the descriptive study we had 85 (85%) male and 15 (15%) female patients having Non Small Cell Lung Cancer (NSCLC). Among them 59 patients were having age 60 and above, 38 patients had age between 40 to 59 and only 3 patients were found in the age group of 20 to 39.

Among 100 NSCLC patients 53 were found with Squamous cell carcinoma histology and 47 were with Adenocarcinoma histology.

49 patients were found in the stage IIIA/IIIB and 51 patients were in stage IV (Metastatic).

Single co morbidity was observed in 70% of patients in co morbid arm where Hypertension 30% was most predominant co morbidity, followed by Diabetes mellitus 22%, Bronchial asthma 8%, COPD 6% and IDH 4% respectively. While multiple co morbidity was observed in 30% of patients in co morbid arm where Hypertension and diabetes mellitus 18% followed by COPD and Hypertension 4%, Diabetes mellitus sand Tb 4% Dibetes mellitus and IDH 2%, COPD and bronchial Asthma 2% respectively.

In the survival analysis non co-morbid arm produces maximum survival (12.79) than co-morbid arm (8.0). This survival difference was measured by Log Rank (Mantel – Cox) test and the result shows a statistically significant *P* value (0.03) which is one of the prominent finding of our study. Sheighet. al. (2012) found a similar relationship in their survival analysis [64]. They found that compared to lung cancer patients without tuberculosis, those with tuberculosis had a significantly shorter average survival duration (584 days vs. 791 days, $P = 0.002$) and a higher mortality hazard ratio (1.30, 95% CI: 1.03 - 1.65). A similar trend was observed in lung cancer patients with diabetes [64].

Stratified data with histology shows another statistically significant result for the superior survival of non co-morbid (10.42) patient having Adenocarcinoma than co-morbid patients (8.0). But there is no significant evidence in the survival analysis in squamous histology.

Non co-morbid patients in both stage IIIA/IIIB and IV tend to have more survival months than co-morbid patients in the respective stage. But there is no statistical evidence to prove

the difference is significant. Although Sheighet. al. (2012) reported that Survival days increased with age (from 580 ± 526 [≤ 50 years] to 803 ± 693 [≥ 71 years] days, p = 0.020) and decreased with stage (from 1224 ± 656 [stage I] to 489 ± 536 [stage IV] days, p<0.001). [64].

Another important finding of our study is non co-morbid patients having age above 60 are likely to have better survival than those of co-morbid patients. Log Rank test shows a *P* value of 0.024 which is highly significant. But those patients in age below 60 are likely to have almost similar survival in both non co-morbid and co-morbid arms but there is not enough statistical significant evidence.

In our study we have also found an increase 1 year and 2 year survival percentage in non co-morbid patients compared to co-morbid patients. We found a one year survival for non comorbid was 36% and for co-morbid was 18%. In a Danish cancer registry analysis it was found that a decrease in one year survival percentage in co-morbid patient [65]. They have reported an increased survival among co-morbid patients 25% to 28% and 33% to 41% for non co-morbid patients registered from 2000 to 2011. So our study shows a similar findings with those reported by Danish cancer registry that is the co-morbidity survival in lung cancer is decreased compared to non comorbidity cases.

7. Conclusion

In our study we have seen that co morbidity is strongly associated with the survival of Non Small Cell Lung Cancer (NSCLC) patient in Bangladesh. Even co morbid elderly people are in great risk of mortality. We have also found a relationship between histology and co morbidity.

8. Limitations

There are few limitations of this study. And these are as follows:

- This study was done in a single cancer center. Thus it does not reflect the complete scenario in our country.
- Sample size was small.

- We could not establish the relationship between survivals based on chemotherapy or treatment pattern as treatment (both chemotherapy and radiotherapy) has an important role in survival. So it was an unintentional confounder in our study.

9. Recommendations for Future Study

In future a multicenter phase III large scale prospective Randomized Clinical Trial (RCT) should be performed to evaluate the actual effect of co morbidity on lung cancer survival in Bangladesh.

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. CA Cancer J Clin 2006;56:106130.

2. Cancer Registry Report; National Institute of Cancer Research & Hospital; 2005-2007.

3. Medical Oncology Bulletin; National Institute of Cancer Research & Hospital, Dhaka, Bangladesh; 2006 & 2007

4. Franco Cavelli- Textbook of Medical Oncology 2nd edition P (173-174)

5. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 1981;66:119 1308.

6. Shopland D. Tobacco use and its contribution to early cancer mortality with a special emphasis on cigarette smoking. Environ Health Perspect 1995;103:131 142.

7. Zienolddiny S, Ryberg D, Arab M, et al. Loss of heterozygosity is related to p53 mutations and smoking in lung cancer. Br J Cancer 2001;84:226 231.

8. Mahabir S, Spitz MR, Barrera SL, et al. Dietary zinc, copper and selenium, and risk of lung cancer. Int J Cancer 2007;1;120(5):1108.

9. Trovo N, Minotel E, Fravelun G. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1992;24:11 16.

10. Hecht S, Hoffmann D. Tobacco-specific nitrosamines, an important group of carcinogens in tobacco and tobacco smoke. Carcinogenesis 1988;17:116 128.

11. Stellman S, Muscat J, Thompson T, et al. Risk of squamous cell carcinoma and adenocarcinoma of the lung in relation to lifetime filter cigarette smoking. Cancer 1997;80:382 388.

12. Thun M, Lally C, Flannery J, et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997;89:1580 1586.

13. M L G Janssen-Heijnen, S Smulders: Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer: Thorax 2004;59:602–607.doi: 10.1136/thx.2003.018044

14. Coebergh JWW, Janssen-Heijnen MLG, Louwman WJ, et al, eds. Cancer incidence, care and survival in the South of the Netherlands, 1955–1999: a report of the Eindhoven Cancer Registry with cross border implications. Eindhoven: Comprehensive Cancer Centre South (IKZ), 2001.

15. Guadagnoli E, Weitberg A, Mor V, et al. The influence of patient age on the diagnosis and treatment of lung and colorectal cancer. Arch Intern Med 1990;150:1485–90.

16. Monfardini S, Aapro M, Ferrucci L, et al. Cancer treatment in the elderly. Eur J Cancer 1993;29A:2325–30.

17. Wei JY. Cardiovascular comorbidity in the older cancer patient. Semin Oncol 1995;22:9–10. 6

18. Greenfield S, Aronow HU, Elashoff RM, et al. Flaws in mortality data. The hazards of ignoring comorbid disease. JAMA 1988;260:2253–5.

19. Asmis TR, Ding K, Seymour L, Shepherd FA, Leighl NB, Winton TL, Whitehead M, Spaans JN, Graham BC, Goss GD: Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2008, 26(1):54–59.

20. Janssen-Heijnen ML, Maas HA, Houterman S, Lemmens VE, Rutten HJ, Coebergh JW: Comorbidity in older surgical cancer patients: influence on patient care and outcome. Eur J Cancer 2007, 43(15):2l179–2193.

21. Lash TL, Thwin SS, Horton NJ, Guadagnoli E, Silliman RA: Multiple informants: a new method to assess breast cancer patients' comorbidity. Am J Epidemiol 2003, 157(3):249–257.

22. Ludbrook JJ, Truong PT, MacNeil M'V, Lesperance M, Webber A, Joe H, Martins H, Lim J: Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? a community based population analysis. Int J Radiat Oncol Biol Phys 2003, 55(5): 1321–1330.

23. Post PN, Kil PJ, Hendrikx AJ, Janssen-Heijnen ML, Crommelin MA, Coebergh JW: Comorbidity in patients with prostate cancer and its relevance to treatment choice. BJU Int 1999, 84(6):652–656.

24. Satariano WA, Ragland DR: The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 1994, 120(2):104–110.

25. Janssen-Heijnen ML, Schipper RM, Razenberg PP, Crommelin MA, Coebergh JW: Prevalence of co-morbidity in lung cancer patients and its relationship with treatment: a population-based study. Lung Cancer 1998,21(2):105–113.

26. Ogle KS, Swanson GM, Woods N, Azzouz F: Cancer and comorbidity: redefining chronic diseases. Cancer 2000, 88(3):653–663.

27. Seshasai SR, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al: Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011, 364 (9):829–841.

28. Van Spronsen DJ, Janssen-Heijnen ML, Breed WP, Coebergh JW: Prevalence of co-morbidity and its relationship to treatment among unselected patients with Hodgkin's disease and non-Hodgkin's lymphoma, 1993- 1996. Ann Hematol 1999, 78(7):315–319.

29. Battafarano RJ, Piccirillo JF, Meyers BF, Hsu HS, Guthrie TJ, Cooper JD, Patterson GA: Impact of comorbidity on survival after surgical resection in patients with stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2002, 123(2):280–287.

30. Budisin E: Comorbidity in Lung Cancer – Operated Patients, Impact on Survival and Prognosis, UICC World Cancer Congress. Washington, DC, USA: Evica Budisin; 2006.

31. Janssen-Heijnen ML, Smulders S, Lemmens VE, Smeenk FW, van Geffen HJ, Coebergh JW: Effect of comorbidity on the treatment and prognosis of elderly patients with non-small cell lung cancer. Thorax 2004, 59(7): 602–607.

32. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P: Impact of comorbidity on lung cancer survival. International journal of cancer Journal international du cancer 2003, 103(6):792–802.

33. Koyi H, Hillerdal G, Branden E: Patient's and doctors' delays in the diagnosis of chest tumors. Lung Cancer 2002, 35(1):53–57.

34. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P: Smoking and lung cancer survival: the role of comorbidity and treatment. Chest 2004, 125 (1):27–37.

35. Hsu NY, Chen CY, Chung KP, Hsu CP, Hsia JY PYW: Pulmonary tuberculosis and lung cancer. Chin Med J 1996, 57(6):S140.

36. Piccirillo JF: Importance of comorbidity in head and neck cancer. Laryngoscope 2000, 110(4):593–602.

37. Bergman L, Dekker G, van Kerkhoff EH, Peterse HL, van Dongen JA, van Leeuwen FE: Influence of age and comorbidity on treatment choice and survival in elderly patients with breast cancer. Breast cancer research and treatment 1991, 18(3):189–198.

38. Firat S, Bousamra M, Gore E, Byhardt RW: Comorbidity and KPS are independent prognostic factors in stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2002, 52(4):1047–1057.

39. Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. Cancer 1997;80:1273– 83.

40. Yancik R. Epidemiology of cancer in the elderly. Current status and projections for the future. Rays 1997;22(Suppl 1):3–9.

41. Doll R, Peto R, Wheatley K, Gray R, Sutherland I. Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 1994; 309:901–11.

42. Peto R, Lopez AD, Boreham J, Thun M, Heath C Jr, Doll R. Mortality from smoking worldwide. Br Med Bull 1996;52:12–21.

43. Goodman MT, Kolonel LN, Wilkens LR, Yoshizawa CN, Le Marchand L. Smoking history and survival among lung cancer patients. Cancer Causes Control 1990;1:155–63.

44. López-Encuentra A, Bronchogenic Carcinoma Co-operative Group. Comorbidity in operable lung cancer: a multicenter descriptive study on 2992 patients. Lung Cancer 2002;35:263–9.

45. van de Schans SA, Janssen-Heijnen ML, Biesma B, Smeenk FW, van de Poll-Franse LV, Seynaeve C, et al. COPD in cancer patients: higher prevalence in the elderly, a different treatment strategy in case of primary tumours above the diaphragm, and worse overall survival in the elderly patient. Eur J Cancer 2007;43:2194– 202.

46. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur J Respir J 2009;34:380–6.

47. Young RP, Hopkins RJ. Link between COPD and lung cancer. Respir Med 2010;104:758–9.

48. Tockman MS, Anthonisen NR, Wright EC, Donithan MG. Airways obstruction and the risk for lung cancer. Ann Intern Med 1987;106:512–18.

49. Wasswa-Kintu S, Gan WQ, Man SFP, Pare PD, Sin DD. Relationship between forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. Thorax 2005;60:570–5.

50. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Respir J 2006;28:1245–57.

51. Derek Grose, Robert Milroy**:** Chronic obstructive pulmonary disease: a complex comorbidity of lung cancer. Journal of Comorbidity 2011;1:45–50.

52. Algar FJ, Alvarez A, Salvatierra A, Baamonde C, Aranda JL, López- Pujol FJ. Predicting pulmonary complications after penumonectomy for lung cancer. Eur J Cardiothorac Surg 2003;23:201–8.

53. Kearney DJ, Lee TH, Reilly JJ, DeCamp MM, Sugarbaker DJ. Assessment of operative risk in patients undergoing lung resection. Importance of predicted pulmonary function. Chest 1994;105:753–9.

54. Sekine Y, Yamada Y, Chiyo M, Iwata T, Nakajima T, Yasufuku K, et al. Association of chronic obstructive pulmonary disease andtumor recurrence in patients with stage IA lung cancer after complete resection. Ann Thorac Surg 2007;84:946–50.

55. Sekine Y, Kesler KA, Behnia M, Brooks-Brunn J, Sekine E, Brown JW. COPD may increase the incidence of refractory supraventricular arrhythmias following pulmonary resection for non-small cell lung cancer. Chest 2001;120:1783–90.

56. Sekine Y, Behina M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. Lung Cancer 2002;37:95–101.

57. Kondo R, Yoshida K, Eguchi T, Kobayashi N, Saito G, Hamanaka K, et al. Clinical features of lung cancer in smokers with light and mildchronic obstructive pulmonary disease: a retrospective analysis of Japanese surgical cases. Eur J Cardiothorac Surg 2011;40:1439–43.

58. López-Encuentra A, Astudillo J, Cerezal J, Gonzalez-Aragoneses F, Novoa N, Sánchez-Palencia A, Bronchogenic Carcinoma Co operative Group of the Spanish Society of Pneumology and Thoracic Surgery. Prognostic value of chronic obstructive pulmonary disease in 2994 cases of lung cancer. Eur J Cardiothorac Surg 2005;27:8–13.

59. C. Martin Tammemagi, Christine Neslund-Dudas, Michael Simoff and Paul Kvale: Impact Of Comorbidity On Lung Cancer Survival: *Int. J. Cancer:* **103,** 792–802 (2003)

60. DeVita V.T., Hallon S., Rosenberg S. *Cancer: Principles and Practice of Oncology 7th Edition*. P: 753-755

61. Abeloff D Martin: Clinical Oncology 3rd Edition; 2004 P-1655

62. Perez CA, Brady LW, Halperin EC. *Principles and Practice of Radiation Oncology: 5th Edition*

63. Ruben Phillip MD; Clinical Oncology- A Multidisciplinary Approval for Physicians and Students. 7th Edition.

64. Cancer Facts and Figures 2013. American Cancer Society. [http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf]

65. Jackman DM, Johnson BE. "Small-cell lung cancer." Lancet (2005); 366(99494):1385-96 [PUBMED]

66. What is non-small cell lung cancer? American Cancer Society (Accessed October 2010).[http://www.cancer.org/Cancer/LungCancer-Non SmallCell/OverviewGuide/lung-cancer--non-small-cell--overview-non-small-cell-lung-cancer]

Patient Consent Form

I _____ hereby give my well informed and conscious consent for participation in the study conducted by Asma Aminul Haque, in the oncology department, Ahsania Mission Cancer Hospital, Mirpur, Dhaka. This study may bring some precious medical information to be useful for me and for human being in future.

I have been informed that written records regarding my illness, treatment and follow up will be kept by by the Investigators.

I am convinced that during participation in the study I will not be exposed to any physical, psychological, social or legal risk. The privacy and confidentiality of mine will be secured. I have read the above which was fully explained to me and give my informed consent for the study.

_____	_____
Signature/Thumb impression of the patient	Signature of principle investigator
Date:	Date:

রোগীর সম্মতিপত্র

আমি _____, আসমা আমিনুল হক পরিচালিত আহছানিয়া মিশন কেন্সার হসপিটাল, মিরপুর, ঢাকায় গবেষণা কার্যক্রমে সম্পূর্ণ সজ্ঞানে এবং সচেতনভাবে অংশগ্রহন করছি। এই গবেষণা বহু মূল্যবান মেডিকেল তথ্য নিয়ে আসবে যা আমার এবং মানবজাতির ভবিষ্যতে উপকারে আসবে।

আমি এও জানাচ্ছি যে গবেষণার জন্য আমার রোগ, চিকিৎসা এবং ফলোআপ গবেষণাকারীর নিকট লিপিবদ্ধ থাকবে।

আমি নিশ্চিত করছি যে, এই গবেষণা চলার সময় আমি কোন রকম শারীরিক, মানসিক এবং বিধিসঙ্গত কোন ঝুঁকির সম্মুখীন হই নি এবং আমার গোপনীয়তা বজায় রাখা হবে।

উপরের উল্লিখিত বিষয় সমূহ আমাকে ব্যাখ্যা করা হয়েছে এবং এই গবেষণা কার্যক্রমে অংশগ্রহণ করার সম্মতি প্রদান করছি।

_____ _____

রোগীর সাইন/ আঙ্গুলের ছাপ

তারিখঃ

প্রধান গবেষকের সাইন

তারিখঃ

Data collection form for "Association of co morbidities with survival of patients with NSCLC"

Name:		**Sex:** ▢**M** ▢**F**	**Age:**
Address:	**Thana:**	**District:**	**Division:**
Contact Number:			
Diagnosis:			**Stage:**
Histology:			
ECOG status:			
Diagnosis date:	**Status** ▢Death ▢ Alive	**Last follow-up date**:	**Death Date**:

Co morbidity:

▢ COPD ▢ CVD ▢ Cerebrovascular disease ▢ Hypertension ▢ DM ▢Others :

Treatment: ▢RT ▢ CT ▢ RT→ CT ▢ Surgery ▢S→ CT ▢ S→ RT→ CT

Regimen	Brand	No. of Cycles	Progression/switch date

Toxicities

▢Anemia ▢Neutropenia ▢Thrombocytopenia ▢ Febrile Neutropenia ▢Fatigue

▢Vomiting ▢Allopecia ▢Others