



Association Between Platelet Count and Other Factors in Patients with Stage-IV Non-Small Cell Lung Cancer

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Abstract: Background: Stage IV non-small-cell lung cancer (NSCLC) means a disease that has spread from the lungs to distant areas of the body like the liver, brain, or bones. An increased platelet count can accompany various cancers including lung cancer. This finding has recently been suggested to indicate a poor prognosis. Preconception on the relation between platelet count and other associated factors in patients with stage-IV non-small cell lung cancer may be a potential associated indicator in managing such patients. Aim of the study: This study aimed to evaluate the relationship between platelet count and other associated factors in patients with stage-IV non-small cell lung cancer (NSCLC). Methods: This prospective observational study was conducted at the National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh during the period from September 2019 to August 2020. A total of 108 patients were enrolled purposively. Detailed history taking and thorough physical examination was done along with relevant investigations. Data were collected by semi-structured questionnaire and analysis was done by SPSS, version 21.0. Results: The mean age of the patients was found 56.4±12.2 years and the majority (79.6%) of patients were male. The highest number of participants (40.7%) were symptomatic; in bed, >50% of the day, almost two-thirds (59.3%) had <5% weight loss, and almost three fourth (69.4%) had squamous cell carcinoma. At the time of the first assessment, 75 (69.4%) patients had normal and 33 (30.6%) had elevated platelet count levels, age, sex, and histological type were statistically not significant between normal and elevated platelet count level groups. But performance status and weight loss were statistically significant ($p<0.05$) between the two groups. According to univariate analysis, age, performance status at presentation, weight loss of more than 10% for 3 months and platelet count before the start of treatment were all significant predictors for overall survival. Conclusion: As per the findings of this study we can conclude that there has no significant correlation of platelet count with age, sex or histological types of NSCLC patients. But with performance status and weight loss, there may have a statistically significant correlation in such patients.

Keywords: Non-Small Cell Lung Cancer, Platelet Count, Prognostic Factor, Stage-IV NSCLC

1. Introduction

Stage IV non-small-cell lung cancer means a disease that has spread from the lungs to distant areas of the body like the liver, brain, or bones. An increased platelet count can accompany various cancers including lung cancer. According to the Global Cancer Statistics 2018 (world), lung cancer is

one of the most common cancers worldwide. This accounts for about 11.6% of total cancer cases. The United States and Eastern Europe show the highest incidence rates of lung cancer among men whereas the highest among women are in North America and Northern Europe [1]. The incidence of lung cancer in both sexes, of all ages, is about 12,374 (8.2%) in 2018 & five-year prevalence is about 11,580 (6.96%) in all

ages, in Bangladesh when compared to other types of cancer. Age-standardized (world) incidence is 9.4% and the mortality rate is 9.0% among the top ten cancers (Global Cancer Observatory, 2018). The 5-year survival rate for lung cancer is around 18%, reflecting a slow but steady improvement from 13.7% in the 1970s [2]. In the late 1990s, this histological shift was first observed in Europe and North America, however, this trend has also been evident in developing nations such as China and India [3, 4]. Surgery, radiotherapy and chemotherapy, targeted therapy and raising immunotherapy remain current treatment options and exhibit limited effectiveness. For stage IV NSCLC without treatment, the median survival time is only 4-5 months with a survival rate at one year of only 10% and the 5-year survival rate is only about 1-2% [5]. In a meta-analysis of 757 NSCLC patients with control of the primary tumor and one to five distant metastases that were all treated with locally ablative therapy, the median OS was 26 months and the 5-year OS was 29% [6]. Thus, although the prognosis in stage IV NSCLC is poor, some carefully selected patients with oligometastatic disease may benefit from aggressive treatment [7]. This helped advise individuals, choose treatment, understand the diseases and optimize the result of chemotherapy [8]. The association between malignancy and increased platelet count has been recognized for almost a century [9]. A prognostic significance between the platelet count and lung cancer has also been identified. Additionally, platelet plays a multifactorial role in cancer progression and metastases. There are also complex interactions between platelets and tumor cells that cause tumor growth, aberrant angiogenesis, invasion, and metastasis [10, 11]. Some studies have revealed thrombocytosis as a paraneoplastic symptom [10, 11] and some studies [12, 13] have reported that increased platelets count are associated with a poor prognosis in various types of cancer, including lung cancer, gastric cancer, pancreatic cancer colorectal cancer, endometrial cancer, ovarian cancer. Some reports have also assessed co-relation of this finding with other clinico-pathological factors (PS, weight loss and histological type), or with survival in patients with lung cancer. Increase platelet count is also associated with various diseases including chronic inflammatory diseases or infectious diseases and iron deficiency anaemia [14]. This study evaluated the implication of other associated factors as a poor prognostic indicator in patients with stage-IV non-small cell lung cancer (NSCLC).

2. Objectives

General objective:

The general objective of this study was to evaluate the relationship between platelet count and other associated factors in patients with stage-IV non-small cell lung cancer (NSCLC).

Specific objectives:

1. To determine the demographic characteristics of the responders.
2. To find out the relationship between increased platelet

count and cancer prognosis.

3. To evaluate the association between increased platelet count with other clinicopathological characteristics in patients with stage-IV NSCLC.
4. To evaluate the association between increased platelet count and median survival in patients with stage-IV NSCLC.

3. Methodology

This prospective observational study was conducted at the National Institute of Cancer Research & Hospital (NICRH), Dhaka, Bangladesh during the period from September 2019 to August 2020. The patients were selected by purposive sampling method. A total of 108 patients were enrolled purposively. Detailed history taking thorough physical examinations were done along with relevant investigations. The total intervention was conducted following the principles of human research specified in the Helsinki Declaration [15] and executed in compliance with currently applicable regulations and the provisions of the General Data Protection Regulation (GDPR) [16].

3.1. Inclusion Criteria

1. Age between 18 to 75 years of age.
2. Stage-IV diseases pathologically confirmed diagnoses of NSCLC.
3. WHO performance status was up from 0 to 4.
4. No prior chemotherapy or radiotherapy.
5. Minimum laboratory criteria (adequate bone marrow function, normal hepatic and renal function).
6. Histological typing of tumors was made according to the recommendation of the WHO.

Exclusion criteria:

1. Patients who had a history of other coexisting or previous cancer.
2. Patients with comorbidities like severe hypertension, splenic diseases and blood coagulation.
3. Patients with a history of whole blood transfusion or any other blood components within 10 days before the blood sample was given.
4. Patients who had taken acetylsalicylic acid drugs one month before the treatment.

3.2. Data Collection Procedure

The sample was selected through inclusion & exclusion methods from the patients who were diagnosed with stage IV NSCLC and came for treatment at NICRH. Those who gave informed written consent was finally enrolled in the study. Data were collected through face-to-face interviews, physical examination, and biochemical, radiological and pathological investigations, from the patients based on the previous report. All the information was documented in the questionnaire. After taking verbal consent from the patients introducing and informing the study purpose and objectives, ensuring privacy and confidentiality by using the questionnaire.

3.3. Data Processing and Analysis

Data were analyzed by using SPSS version 21.0 and MS Excel 2010. Continuous data were expressed by mean, and standard deviation and categorical data were expressed by percentages and frequency. Data were presented in tabular or graphic form. A p-value <0.05 was considered significant. Statistical analysis was done by using an appropriate statistical tool like “the chi-square” test, where applicable. Statistical significance was set as 0.05 level & confidence interval at 95% level. Median survival was analyzed by Kaplan-Meier analysis.

3.4. Ethical Consideration

Formal ethical clearance was taken from the IRB of the NICRH for conducting the study. Proper permission was taken from the department concerned with the study.

4. Results

In this study, among the total 108 participants, 80% were male whereas the rest 20% were female. So male participants were dominating in number and the male-female ratio was 4:1. In analyzing the ages of the participants we observed that almost two thirds (62.0%) of patients had <60 years. The mean age was found 56.4 ± 12.2 years with a range from 35-75 years. As per the performance status WHO of the study patients, it was observed that the majority (40.7%) of patients had symptomatic; in bed >50% of the day followed by 29 (26.9%) had symptomatic; in bed <50% of the day, 18 (16.7%) symptomatic; fully ambulatory and 17 (15.7%) had bedridden. Among total patients, more than half (59.3%) patients were with <5% weight loss followed by 31 (28.7%) with a loss of 5-10% and the rest 13 (12.0%) with a loss of >10%. More than two third (69.4%) of our patients had squamous cell carcinoma and 33 (30.6%) had adenocarcinoma but not found large cells. In our study at baseline, 75 (69.4%) patients had normal and 33 (30.6%) had elevated platelet count levels. In 1st follow-up after 12 weeks, 62 (72.1%) had normal and 24 (27.9%) had elevated platelet count levels. In 2nd follow-up after 24 weeks, 48 (76.2%) had normal and 15 (23.8%) had elevated platelet count levels. In 3rd follow-up after 36 weeks, 38 (79.2%) had normal and 10 (20.8%) had elevated platelet count levels. At baseline, 47 (62.7%) patients (Age<60 years) had normal and 20 (60.6%) had elevated platelet count level. At 1st follow-up, 41 (66.2%) patients (Age<60 years) had normal and 15 (62.5%) had elevated platelet count level, at 2nd follow-up 36 (75.0%) patients (Age<60 years) had normal and 12 (80.0%) had elevated platelet count level and at 3rd follow-up 31 (81.6%) patients (Age<60 years) had normal and 6 (60.0%) had elevated platelet count level. The differences were statistically not significant ($p>0.05$) between the two groups. In assessing the association between platelet counts with the performance of WHO in different follow-ups we observed that, at baseline, the majority (45.3%) of patients had symptomatic; in bed,>50% of the day in normal and 10 (30.3%) had elevated platelet count level. During 1st follow-up,

26 (40.6%) patients were symptomatic; in bed,>50% of the day in normal and 5 (20.8%) had elevated platelet count levels, at 2nd follow-up, 26 (54.2%) patients had symptomatic; in bed,>50% of the day in normal and 3 (20.0%) had elevated platelet count level. At 3rd follow-up, 19 (50.0%) patients had symptomatic; in bed,>50% of the day in normal and 1 (10.0%) had an elevated platelet count level. The differences were statistically significant ($p<0.05$) between the two groups. In assessing the association between platelet counts with weight loss in different follow-ups we observed that, at baseline, more than two third (69.3%) of patients had <5% weight loss in normal and 12 (36.4%) had elevated platelet count levels. During 1st follow-up, 42 (70.0%) patients had <5% weight loss in normal and 10 (29.4%) had elevated platelet count levels, at 2nd follow-up, 34 (70.8%) patients had <5% weight loss in normal and 5 (33.3%) had elevated platelet count level. In at 3rd follow-up, 33 (86.8%) patients had 5-10% weight loss in normal and 5 (50.0%) had elevated platelet count levels. The differences were statistically significant ($p<0.05$) between the two groups. In assessing the association between platelet counts with histological type in different follow-ups we observed that at baseline almost two third (69.3%) of patients had SCC in normal and 23 (69.7%) had elevated platelet count levels. At the 1st follow-up, 46 (71.0%) patients had SCC in normal and 18 (75.0%) had elevated platelet count levels, at 2nd follow-up, 35 (72.9%) patients had SCC in normal and 12 (80.0%) had elevated platelet count level. At 3rd follow-up, 28 (73.7%) patients had SCC in normal and 8 (80.0%) had elevated platelet count levels. The differences were statistically not significant ($p>0.05$) between the two groups.

Table 1. Distribution of the study patients by WHO performance status (N=108).

Performance status WHO	n	%
0 (Asymptomatic)	0	0.0
1 (Symptomatic; fully ambulatory)	18	16.7
2 (Symptomatic; in bed < 50% of day)	29	26.9
3 (Symptomatic; in bed > 50% of day)	44	40.7
4 (Bedridden)	17	15.7

Table 2. Distribution of the study patients by weight loss (N=108).

Weight loss (%)	n	%
<5 %	64	59.3
5-10 %	31	28.7
>10 %	13	12.0

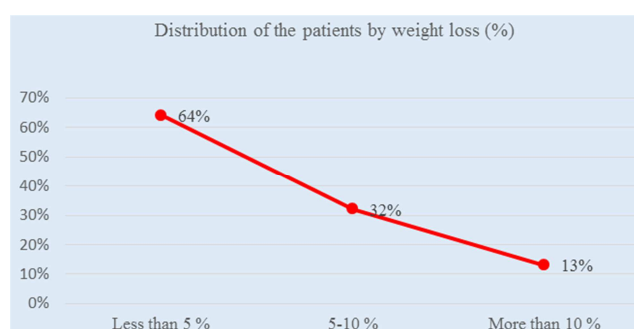
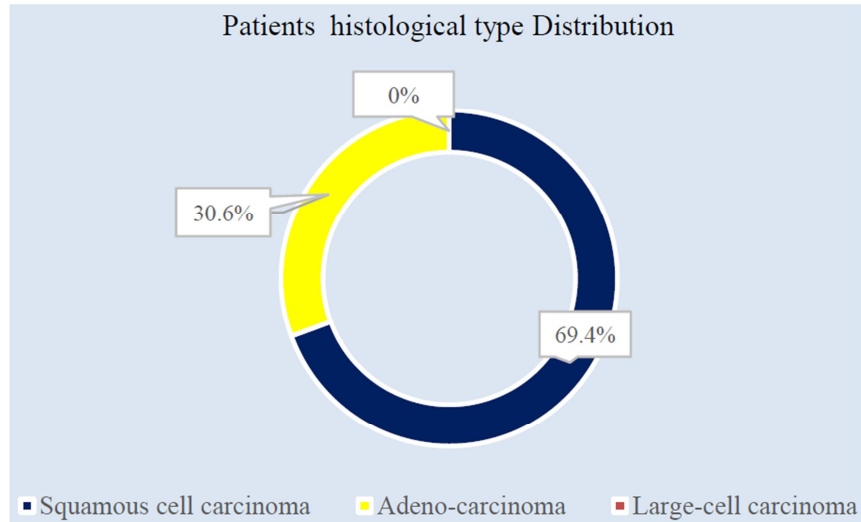


Figure 1. Liner chart showed the weight loss of the patients. (N=108).

Table 3. Distribution of the study patients by histological type (N=108).

Histological type	n	%
Squamous cell carcinoma	75	69.4
Adenocarcinoma	33	30.6
Large-cell carcinoma	0	0.0

**Figure 2.** Ring diagram showed the distribution of the study patients by histological type. (N=108).**Table 4.** Association between platelet count levels in different follow-ups. (N=108).

Platelet count per mcL	n	%
At baseline (N=108)		
≤450000 (Normal)	75	69.4
>450000 (Elevated)	33	30.6
1st follow-up after 12 weeks (n=86)		
≤450000 (Normal)	62	72.1
>450000 (Elevated)	24	27.9
2nd follow-up after 24 weeks (n=63)		
≤450000 (Normal)	48	76.2
>450000 (Elevated)	15	23.8
3rd follow-up after 36 weeks (n=48)		
≤450000 (Normal)	38	79.2
>450000 (Elevated)	10	20.8

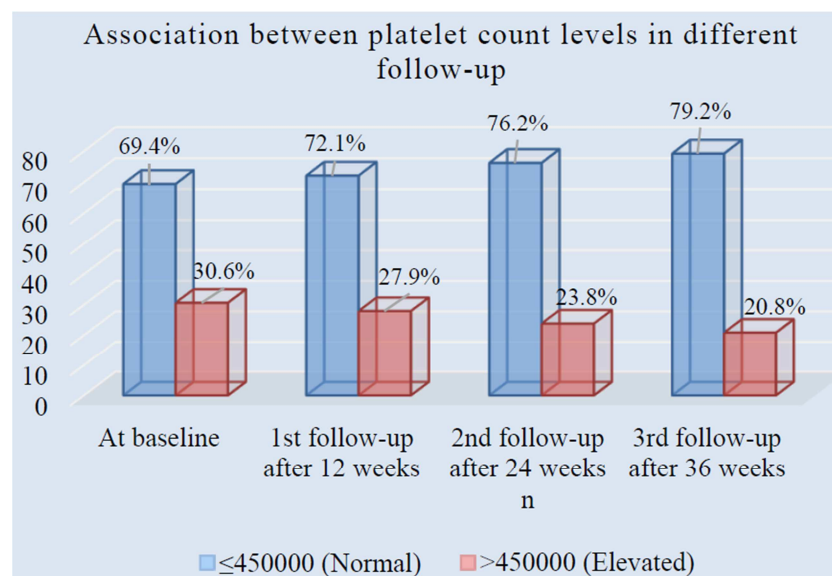
**Figure 3.** Bar chart of platelet count level in different follow-ups. (N=108).

Table 5. Association between platelet count level with age in different follow-ups. (N=108).

Age (Year)	Platelet count per mL				P value
	(Normal) ≤450000		(Elevated) >450000		
	n	%	n	%	
At baseline (n=75/33)					
<60 yrs.	47	62.7	20	60.6	0.731
≥60 yrs.	28	37.3	13	39.4	
At 1 st follow-up (n=62/24)					
<60 yrs.	41	66.2	15	62.5	0.731
≥60 yrs.	21	32.8	9	37.5	
At 2 nd follow-up (n=48/15)					
<60 yrs.	36	75.0	12	80.0	0.162
≥60 yrs.	12	25.0	3	20.0	
At 3 rd follow-up (n=38/10)					
<60 yrs.	31	81.6	6	60.0	0.125
≥60 yrs.	7	18.4	4	20.0	

Table 6. Association between Platelet counts with the performance of WHO in different follow-ups. (N=108).

Performance of WHO	Platelet count (per mL)				P value
	(Normal) ≤450000		(Elevated) >450000		
	n	%	n	%	
At baseline (n=75/33)					
0 (Asymptomatic)	0	0.0	0	0.0	0.003
1 (Symptomatic; fully ambulatory)	6	8.0	12	36.4	
2 (Symptomatic; in bed < 50% of day)	23	30.7	6	18.2	
3 (Symptomatic; in bed > 50% of day)	34	45.3	10	30.3	
4 (Bedridden)	12	16.0	5	15.1	
At 1 st follow-up (n=62/24)					
0 (Asymptomatic)	0	0	0	0.0	0.017
1 (Symptomatic; fully ambulatory)	10	15.6	4	16.7	
2 (Symptomatic; in bed < 50% of day)	20	31.3	6	25.0	
3 (Symptomatic; in bed > 50% of day)	26	40.6	5	20.8	
4 (Bedridden)	6	9.7	9	37.5	
At 2 nd follow-up (n=48/15)					
0 (Asymptomatic)	0	0	0	0	0.012
1 (Symptomatic; fully ambulatory)	6	8.3	6	40.0	
2 (Symptomatic; in bed < 50% of day)	14	29.2	5	33.3	
3 (Symptomatic; in bed > 50% of day)	26	54.2	3	20.0	
4 (Bedridden)	2	4.2	1	6.7	
At 3 rd follow-up (n=38/10)					
0 (Asymptomatic)	0	0.0	0	0.0	0.023
1 (Symptomatic; fully ambulatory)	3	7.9	4	40.0	
2 (Symptomatic; in bed < 50% of day)	14	36.8	5	50.0	
3 (Symptomatic; in bed > 50% of day)	19	50.0	1	10.0	
4 (Bedridden)	2	5.3	0	0.0	

Table 7. Association between Platelet count with weight loss in different follow-ups. (N=108).

Weight loss (%)	Platelet count (per mL)				P value
	(Normal) ≤450000		(Elevated) >450000		
	n	%	n	%	
At baseline (n=75/33)					
<5%	52	69.3	12	36.4	0.001
5-10%	18	24.0	13	39.4	
>10%	5	6.7	8	24.2	
At 1 st follow-up (n=62/24)					
<5%	42	70.0	10	29.4	0.003 ^s
5-10%	16	26.7	6	17.6	
>10%	4	6.7	8	23.5	
At 2 nd follow-up (n=48/15)					
<5%	34	70.8	5	33.3	0.033
5-10%	11	22.9	8	53.3	
>10%	3	6.3	2	13.3	
At 3rd follow-up (n=38/10)					
<5%	4	10.5	3	30.0	0.026
5-10%	33	86.8	5	50.0	
>10%	1	2.6	2	20.0	

Table 8. Association between Platelet counts with histological type in different follow-ups. (N=108).

Histological type	Platelet count (per mL)				P value
	(Normal)≤450000		(Elevated) >450000		
	n	%	n	%	
At baseline (n=75/33)					
Squamous cell carcinoma	52	69.3	23	69.7	0.969
Adenocarcinoma	23	30.7	10	30.3	
Large-cell carcinoma	0	0.0	0	0.0	
At 1 st follow-up (n=62/24)					
Squamous cell carcinoma	44	71.0	18	75.0	0.769
Adenocarcinoma	18	29.0	6	25.0	
Large-cell carcinoma	0	0.0	0	0.0	
At 2 nd follow-up (n=48/15)					
Squamous cell carcinoma	35	72.9	12	80.0	0.582
Adenocarcinoma	13	27.1	3	20.0	
Large-cell carcinoma	0	0.0	0	0.0	
At 3 rd follow-up (n=38/10)					
Squamous cell carcinoma	28	73.7	8	80.0	0.681
Adenocarcinoma	10	26.3	2	20.0	
Large-cell carcinoma	0	0.0	0	0.0	

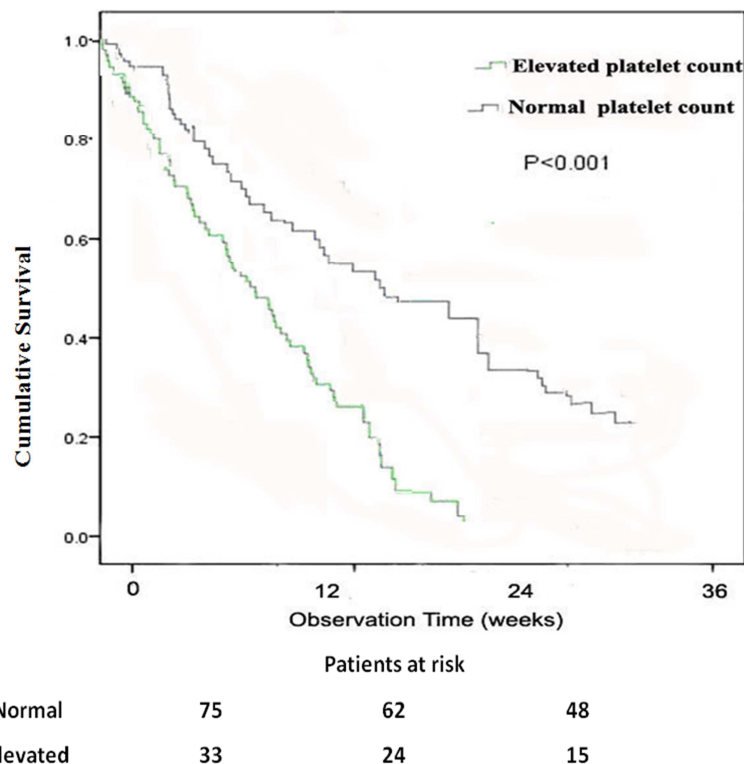
**Figure 4.** Survival difference between the normal and the elevated platelet count level group. Platelet count level; elevated, standard NSCLC patients.

Figure 4 Kaplan-Meier shows stage-IV NSCLC at first presentation median survival (MS) time in these patients was significantly shorter compared with patients without thrombocytosis. The MS time significantly higher for patient's normal platelet count group than the elevated platelet count group (7.5 months vs. 5.5 months), respectively (95% CI, 5.5-7.5), $P < 0.001$.

5. Discussion

This study aimed to evaluate the relationship between platelet count and other associated factors in patients with stage-IV non-small cell lung cancer (NSCLC). In this study, it

was observed that almost two-thirds (62.0%) of patients were from the <60 year's age group. The mean age was found 56.84 ± 12.2 years with a range from 35-75 years. The majority (79.6%) of patients were male and 22 (20.4%) were female. A similar study [17] found the median age of patients was 62.7 years (range 39-76 years) and 51% of patients were >60 years. Another study also found mean age of 58.3 ± 8.99 (range 36-79) years and there were (73.6%) males and (26.4%) females [18]. Cui et al. (2017) [19] found that (65.6%) of patients were male and (34.4%) were female. This study showed an association between platelet counts and the age of the study patients, it was observed that, at baseline, 47 (62.7%) patients' age was <60 years, had normal and 20 (60.6%) had elevated platelet

count levels. During 1st follow-up, 41 (66.2%) patients of <60 years had normal and 15 (62.9%) had elevated platelet count levels, at 2nd follow-up, 36 (75.0%) patients of <60 years had normal and 12 (80.0%) had elevated platelet count level. In 3rd follow-up, 31 (81.60%) patients of <60 years had normal and 6 (60.0%) had elevated platelet count levels. The difference was statistically not significant ($p>0.05$) between the two groups which was similar to the study conducted by Aoe *et al.* (2014) [20]. In the current study, it was observed that the majority (40.7%) of patients had symptomatic; in bed >50% of the day followed by 29 (26.9%) had symptomatic; in bed <50% of the day, 18 (16.7%) symptomatic; fully ambulatory and 17 (15.7%) had bedridden. This study also showed an association between platelet count and the PS of WHO. At baseline, a good number (45.3%) of patients had symptomatic; in bed >50% of the day had normal and 10 (30.3%) had elevated platelet count levels. In at 1st follow-up, 26 (40.6%) patients had symptomatic; in bed >50% of the day had normal and 5 (20.8%) had elevated platelet count levels. In at 2nd follow-up, 26 (54.2%) patients had symptomatic; in bed >50% of the day had normal and 3 (20.0%) had elevated platelet count levels. In at 3rd follow-up, 19 (50.0%) patients had Symptomatic; in bed > 50% of the day had normal and 1 (10.0%) had an elevated platelet count level. The differences were statistically significant ($p<0.05$) between the two groups which were similar to the study conducted by Davidov (2014) [17] and Maráz *et al.* (2013) [18]. Besides these, it was observed that more than half (59.3%) of the patients had <5% weight loss followed by 31 (28.7%) had a loss of 5-10% and 13 (12.0%) had a loss of >10%. This current study also showed an association between platelet count with weight loss. At baseline, more than two third (69.3%) of our patients with <5 percent weight loss had normal and 12 (36.4%) had elevated platelet count levels. At 1st follow-up, 42 (70.0%) patients with <5 percent weight loss had normal and 10 (29.4%) had elevated platelet count levels, at 2nd follow-up, 34 (70.8%) patients with <5 percent weight loss had normal and 5 (33.3%) had elevated platelet count level and at 3rd follow-up, 33 (86.8%) patients with 5-10 percent weight loss had normal and 5 (50.0%) had elevated platelet count level. The differences were statistically significant ($p<0.05$) between the two groups. It is similar to the study conducted by Davidov (2014) [17]. In this study, more than two third (69.4%) of patients had squamous cell carcinoma and 33 (30.6%) had adenocarcinoma but not found large cell carcinoma. At baseline, almost two-thirds (69.3%) of patients had SCC in normal and 23 (69.7%) had elevated platelet count levels. At the 1st follow-up, 46 (71.9%) patients had SCC in normal and 18 (75.0%) had elevated platelet count levels. At 2nd follow-up, 35 (72.9%) patients had SCC in normal and 12 (80.0%) had elevated platelet count levels and at 3rd follow-up, 28 (73.7%) patients had SCC in normal and 8 (80.0%) had elevated platelet count level. The differences were statistically not significant ($p>0.05$) between the two groups. These findings are similar to the study done by Davidov (2014) [17] and Maráz *et al.* (2013) [18]. In this study, at baseline 75 (69.4%) patients had normal and 33 (30.6%) had elevated platelet count levels. In

1st follow-up after 12 weeks, 62 (72.1%) had normal and 24 (27.9%) had elevated platelet count levels. In 2nd follow-up after 24 weeks, 48 (76.2%) had normal and 15 (23.8%) had elevated platelet count level. In 3rd follow-up after 36 weeks, 38 (79.2%) had normal and 10 (20.8%) had elevated platelet count levels. These findings are similar to the study done by Davidov (2014) [17] and Maráz *et al.* (2013) [18]. The results of the univariate analysis were summarized in age, performance status at presentation, weight loss of more than 10% for 3 months and platelet count before the start of chemotherapy were all significant predictors for the overall survival. It was similar to the study conducted by Davidov (2014) [17] and Cui *et al.* (2017) [19]. The results of multivariate analysis including all variables for which $p<0.05$ on univariate analysis were summarized of the variables that were included in the multivariate analysis age, performance status, and elevated platelet count at presentation were independent prognostic determinants for overall survival. It was similar to the study conducted by Davidov (2014) [17] and Cui *et al.* (2017) [19].

6. Limitations of the Study

The study population was selected from one selected hospital in Dhaka city in Bangladesh. So, the results of the study may not be reflecting the exact picture of the whole country. On the other hand, the present study was conducted in a very short period. The small sample size was also a limitation of the present study. Recall bias could not be excluded.

7. Conclusion and Recommendation

As per the findings of this study, we can conclude that there has no significant correlation between platelet count and age, sex or histological types of NSCLC patients. But with performance status and weight loss, there may have a statistically significant correlation in such patients. Noted that, in this study, as per the univariate analysis age, performance status at presentation, weight loss for more than 10% for 3 months and platelet count before the start of treatment were found as significant predictors for overall survival. Considering all, elevated platelet count may be taken as an effective associated factor for survival in patients with stage-IV NSCLC.

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