Myanmar Health Sciences Research Journal, Vol. 30, No. 2, 2018

Relationship between Coagulation Parameters and Disease Severity in Patients with Primary Lung Cancer

Khin La Pyae Tun[1], Win Pa Pa Naing[1], Myo Myint Maw[2], Aye Mya Khaing[1], Wai Wai Han[1], Ni Ni Win[1], Win Win Mar[1] & Khin Saw Aye[1]*

[1]Department of Medical Research
[2]Yangon General Hospital

Activation of coagulation and fibrinolysis is frequently encountered among cancer patients. Such tumors are supposed to be associated with higher risk of invasion, metastasis and eventually worse outcome. This study was aimed to find out the relationship between coagulation parameters and diseases severity in primary lung cancer patients. A total of 103 primary lung cancer patients attending the Out-patient Department of Medical Oncology Unit, Yangon General Hospital, were involved in the study. The median age was 59 years (range from 13 to 82 years) with male to female ratio of 1.8:1. Among them, 81% of lung cancer patients had history of smoking. Regarding the primary site of the tumour, 64% (66) of cases had right sided lung cancer and 36% (3.7) had left sided tumours. Pretreatment blood coagulation tests including fibrinogen level, prothrombin time (INR) and platelet count were determined by using automated blood coagulation analyzer CA-50 Sysmex. In one year study, according to revised WHO classification of the lung tumours, 7(6.8%) of the tumours were small cell lung cancer, 51(49.5%) squamous cell carcinoma, 35(34%) adenocarcinoma, 10(9.7%) other types (large cell carcinoma and anaplastic carcinoma). According to TNM staging, 4 cases (3.9%) were stage I, 14(13.6%) stage II, 35(34%) stage III and 50(48.5%) were stage IV. The plasma level of all coagulation tests revealed statistically significance in correlation to advanced (stage III and IV) stage of lung cancer, plasma fibrinogen level ($p<0.0001$), prothrombin time ($p=0.007$), INR ($p=0.002$) and platelet count ($p=0.009$), respectively. However, histological types of lung cancer were not significantly associated with coagulation parameters. Therefore, this study pointed out that the high levels of coagulation parameters were associated with the advanced cancer staging and these parameters might be used as the predictors for disease severity of primary lung cancer patients.

Key words: Lung cancer, Coagulation parameters

INTRODUCTION

Lung cancer is the most frequent occurring cancer and leading cause of cancer death worldwide.[1] Patients with malignant tumors often have systemic blood coagulation dysfunction, the relationship between cancer and coagulation is characterized by several mechanism pointing that tumour biology and coagulation are closely linked process.[2] It is now well-established that clotting activation is frequently encountered in cancer, typically manifestation as a low grade DIC or venous thrombloembolism either due to cancer itself or agents used for treatment. Patients with tumours of the lungs, pancrease and GI tract are supposed to be more prone to hypercoagulable state.[3] Tumours activating coagulation system supposed to behave more aggressively with higher risk of invasion and metastasis. Approximately 90% of cancer patients with metastasis disease and half of all cancer

*To whom correspondence should be addressed.
Tel: +95-95161285
E-mail: klapyaetun@gmail.com

patients have abnormal coagulation parameters. The most common abnormalities in cancer patients are elevation of the clotting factors V, VIII, IX and XI, increased fibrin degradation products (FDP), hyperfibrinogenaemia and thrombocytosis.[4]

Fibrinogen, the most abundant plasma coagulation factor is synthesized by hepatocytes. The formation of platelet-fibrin-tumour cell aggregates may cause adhesion to endothelial cells and confers metastasis potential.[5] High levels of circulating biomarkers resembling activated coagulation and fibrinolytic system such as fibrinogen, fibrinogen split products and D-dimer have been associated with decreased survival for several tumour types in previous studies.[6-9] Research activities among lung cancer patients investigating the relationship between activated homeostasis system and prognosis have revealed similar results.[10-13]

Therefore, this study aimed to investigate the incidence of some coagulation parameters abnormalities in primary lung cancer patients and attempted to evaluate the correlation of these coagulation tests with other clinic-pathologic variables.

MATERIALS AND METHODS

This study comprised 103 primary lung cancer patients with inclusion criteria of histologically or cytologically confirmed primary lung cancer before taking chemo or radio therapy in last 6 months. Exclusion criteria included patients with history of bleeding disorder, patients who were taking anticoagulants for thromboembolic disease and patients with secondary metastasis to lung. A total of 103 primary lung cancer patients (male to female ratio with 1.8:1) attended the Out-patients Department of Medical Oncology Unit, YGH from January to September, 2016 were eligible for inclusion criteria in this study.

The pathological diagnosis of lung cancer was established in accordance with the revised WHO classification of lung tumours[14] and staged relying on TNM staging for lung cancer.[15] The pretreatment evaluation included detailed clinical history, series of biochemistry tests, complete blood cell counts and coagulation tests. Results of the investigation including Chest X-ray, USG, bronchoscopy and computed tomography were noted.

Coagulation assays

Two milliliters of venous blood sample were collected in sodium citrate tube before initiation of chemo or radiation therapy for measurement of coagulation parameters. The samples were taken to Blood Research Division, Department of Medical Research and centrifuged immediately. Within 3-4 hours after collection, plasma fibrinogen level and prothrombin time (INR) were determined by using CA-50 automated blood coagulation analyzer, Sysmex were used to measure prothrombin time (INR) (SIEMENS, Thromborel ^{R} S kit) and plasma fibrinogen level (SIEMENS, Dade^{R} Fibrinogen Determination Reagents).

Statistical analysis

Being a descriptive study, frequency and proportion for categorical data and mean and SD for continuous data were used to summarize the data. Chi square test and 't' test were used to find out the relationship between coagulation parameters and histological types and staging of the primary lung cancer. Statistical analysis was carried out using SPSS 22 software. The ‘p’ value of <0.05 was regarded as statistically significance.

Ethical consideration

This proposal was approved by Ethics Review Committee, Department of Medical Research. Informed consent was taken from all patients prior to the commencement of the study.

RESULTS

Characteristics of the patients

A total of 103 patients with a pathologically confirmed primary lung cancer were enrolled in our study. Baseline histopathological characteristics and demographic features of patients are shown in Table 1.

Table 1. Patient characteristics

Description	No. of patients	Percent
Total no of lung cancer patients	103	100
Age (years)	59	
Median (range)	(13-82)	
Gender		
Male	67	65
Female	36	35
History of smoking		
Positive	83	81
Negative	20	19
Site of primary tumour		
Right sided	66	64
Left sided	37	36
Haemoglobin level (g/dl), Mean±SD	11.69±2.12	
Total white cell count (WBC) (10^9/L)	10.43±3.89	
Creatinine (mg/dl)	72.99±20	

Table 2. Coagulation variables (n=103)

Coagulation tests	Reference range	Low (%)	Normal (%)	High (%)
Plasma fibrinogen level	150-375 mg/dl	-	73(70.9)	30(29.1)
Prothrombin time	11-14 seconds	4(3.9)	52(50.5)	47(45.6)
INR	0.9-1.2	4(3.9)	58(56.3)	41(39.8)
Platelet count	150-400x10^3/µl	-	73(70.9)	30(29.1)

Median age at diagnosis was 59 years old, ranged 13-82 years, where males constituted majority of the group (n=100, 63%). A total of 83(81%) of patients had the history of smoking. Regarding the primary site of tumors, 66 of cases (64%) were right- sided and 37(36%) were left-sided tumors.

According to revised WHO classification of the lung tumors, 7(6.8%) of the tumors were small cell lung cancer, 51(49.5%) squamous cell carcinoma, 35(34%) adenocarcinoma, 10(9.7%) other types (large cell carcinoma and anaplastic CA).

According to TNM staging for lung cancer, 4 of the cases (3.9%) were stage I, 14(13.6%) stage II, 35(34%) stage III and 50(48.5%) were stage IV. The values of coagulation variables are shown in Table 2. The coagulation tests and their correlation with histological types of primary lung cancer are described in Table 3. The relationship between coagulation parameters and the histological types of lung cancer are summarized in Table 3.

There was no statistically significant relationship between them. In Table 4, it was observed that there was a statistically significant association between all the coagulation parameters and stages of lung cancer. Patients with advanced (extensive) stages of lung cancer exhibited evidently higher level of plasma fibrinogen, platelet counts and prothrombin time (INR). ($p<0.0001$*, $p=0.009$*, $p=0.007$*, $p=0.002$*, respectively).

Table 3. Relationship between coagulation parameters and histological types of lung cancer

Histological types of lung cancer	Coagulation tests n(%)							
	Platelet count (p=0.37)		Plasma fibrinogen level (p=0.85)		Prothrombin time (p=0.79)		INR (p=0.78)	
	Normal	High	Normal	High	Normal	High	Normal	High
Small cell carcinoma	3 (42.9)	4 (57.1)	3(42.9)	4(57.1)	5(71.4)	2(28.6)	5(71.4)	2(28.6)
Squamous cell carcinoma	37(72.6)	14(27.4)	26(51.0)	25(49.0)	28(54.9)	23(45.1)	32(62.8)	19(37.2)
Adenocarcinoma	25(71.4)	10(28.6)	15(42.9)	20(57.1)	18(51.4)	17(48.6)	20(57.1)	15(42.9)
Others	8(80.0)	2(20.0)	4(40.0)	6(60.0)	5(50.0)	5(50.0)	5(50.0)	5(50.0)

Table 4. Relationship between coagulation parameters and stages of lung cancer

Stages of lung cancer	Coagulation tests n (%)							
	Platelet count (p=0.009*)		Plasma fibrinogen level (p<0.0001*)		Prothrombin time (p=0.007*)		INR (p=0.002*)	
	Normal	High	Normal	High	Normal	High	Normal	High
Stage I	4(100.0)	0	4(100.0)	0	4(100.0)	0	4(100.0)	0
Stage II	13(92.9)	1(7.1)	13(92.9)	1(7.1)	12(85.7)	2(14.3)	14(100.0)	0
Stage III	28(80.0)	7(20.0)	19(54.3)	16(45.7)	19(54.3)	16(45.7)	20(57.1)	15(42.9)
Stage IV	28(56.0)	22(44.0)	1(24.0)	38(76.0)	21(42.0)	29(58.0)	24(48.0)	26(52.0)

'p' value of <0.05 was regarded as statistically significant.

DISCUSSION

A systemic activation of clotting system has been observed in cancer patients which is usually reflected by subclinical abnormalities of conventional coagulation tests.[16, 17] There were some evidences that activation of coagulation system by neoplastic cells facilitates invasiveness and metastasis.[13] Thus, the extend of such activation has been associated with tumor stage and prognosis in some malignancies such as breast, colorectal and lung cancers.[8, 18, 19] As the occurrence of the lung cancer is strongly associated with the smoking, a total of 83(81%) of the patients had history of smoking in this study. Most of the patients were found to be in advanced stages, 35(34%) of the cases were stage III and 50 cases (48.5%) were in Stage IV. Thrombocytosis, hyper-fibrinogenemia and elevated D-dimer levels have been demonstrated in different types of cancer involving head and neck, colon, prostate and lung cancer.[20, 21]

Pedersen, *et al.*[22] reported increased platelet count in 32% of 1,115 patients with primary lung cancer, and showed that thrombocytosis was prognostically significant. In 2013, Faruk Tas, *et al.*[23] found that patients with extensive stage SCLC exhibited evidently higher levels of D-dimer, INR and platelet count. In this study, increased in platelet count above $400x10^3$, was found in 30 cases (29.1%) among 103 patients and increased in platelet was statically significantly associated with advanced stages of the lung cancer (p=0.009). Fibrinogen, one of the major protein, is synthesized in the liver and secreted into the circulation. Although fibrinogen synthesis is significantly up regulated by inflammatory stimulation, the precise mechanism in malignancy has not been elucidated yet.

Inflammatory cytokines such as IL6 secreted from cancer cells are supposed to induce production of fibrinogen from the liver. Thus, hypersecretion of fibrinogen may overcome depletion of coagulation tests by ongoing DIC process.[24] Meehan, *et al.*[25] studied 119 untreated SCLC patients and showed that higher pretreatment fibrinogen levels correlated significantly with advanced stages of the disease and reduced survival. Pavey, *et al.*[26] and Maeda, *et al.*[27] found that plasma fibrinogen was associated with decreased survival and also strongly with stages of NSCLC.

So, these findings are in concordance with the study[25] that high pretreatment plasma fibrinogen level was strongly correlated with the advanced (extensive) stage of lung cancer ($p<0.0001$) and also found that 55 patients (53.4%) of lung cancer patients have high pretreatment plasma fibrinogen level. However, the survival analysis was not studied because of limitation of time and budget. The coagulation cascade initiated by tissue factors (procoagulants) triggers a number of events which in turns converts prothrombin to thrombin and generates the insoluble fibrin clots. Assuming that fibrinogen level is normal, a prolong prothrombin time signifies deficiency, depletion of coagulation factors or presence of a specific inhibitor in this cascade.[28]

Prolongation of PT was strongly associated with poor prognosis in NSCLS (Non-small cell lung cancer) patients in previous study but in that report multivariate did not confirm the prognostic relevance of any coagulation factors.[29] The study had also revealed the significance of prolong prothrombin time (INR) in correlation with advanced stages of the lung cancer p-0.007 (p-0.002). In clinical practice, prolongation of PT with a PTT due to depletion of coagulation tests is a well-known markers for DIC.[30] A total of 47 cases (45.6%) of primary lung cancer patients had prolong prothrombin time (INR) in this study. Therefore, this finding supports the presence of low-grade DIC in lung cancer patients. A number of studies have also shown relationship between coagulation changes and natural history of malignancies. Studies conferring evidence of anticoagulants

for cancer patients have revealed conflicting results. However, anticoagulants, particularly heparin with low molecular weight have an anti-tumour effect without fatal bleeding and venous thromboembolism.[31]

This study was a descriptive study and information on post treatment coagulations parameters and survival analysis had not emphasized. A prospective study is required to determine the prognostic significance of coagulation parameters. Anyway, in the present study, extensive (advanced) stages of disease were strongly associated with each of the coagulation parameters (platelet count, fibrinogen level, PT(INR), respectively, although the histological types of lung cancer were not correlated with them. Further large studies on specific subgroups of lung cancer are needed to better define the effective prognostic values of the clotting abnormalities and we may recommend the use of coagulation assays particularly, fibrinogen, PT (INR) in all new lung cancer patients to provide the foresight about outcome, so constitute a surrogate marker for treatment with novel anticoagulants in the near future.

REFERENCES

1. GLOBOCAN 2012: Cancer incidence and mortality worldwide. [Internet]. Available from: http://www. globocan.iarc
2. Lyman GH & Khorana AA. Cancer, clots and consensus: New understanding of an old problem. Journal of Clinical Oncology 2009; 27(29): 4821-6.
3. Gouin-Thibault I & Samama MM. Laboratory diagnosis of the thrombophilic state in cancer patients. In: Seminars in Thrombosis and Hemostasis 1999; 25(02): 167-172.
4. Dvorak HF. Thrombosis and cancer. Human Pathology 1987; 1(8): 275-84.
5. Biggerstaff JP, Seth N, Amirkhosravi A, Amaya M, Fogarty S, Meyer TV, et al. Soluble fibrin augments platelet/tumor cell adherence in vitro and in vivo and enhances experimental metastasis. Clinical & Experimental Metastasis 1999; 17(8): 723-730.
6. Oberhoff C, Rollwagen C, Tauchert AM, Hoffmann O, Winkler UH & Schindler AE. Perioperative development of a thrombogenic risk profile in patients with carcinomas of the breast: A cause of increased thrombosis. European Journal of Gynaecological Oncology 2000; 21(6): 560-568.
7. Miller B & Heilmann L. Hemorheologic variables in breast cancer patients at the time of diagnosis and during treatment. Cancer 1988; 62(2): 350-354.
8. Oya M, Akiyama Y, Okuyama T & Ishikawa H. High preoperative plasma D-dimer level is associated with advanced tumor stage and short survival after curative resection in patients with colorectal cancer. Japanese Journal of Clinical Oncology 2001; 31(8): 388-394.
9. Bottasso B, Mari D, Coppola R, Santoro N, Vaglini M & Mannucci PM. Hypercoagulability and hyperfibrinolysis in patients with melanoma. Thrombosis Research 1996; 81(3): 345-352.
10. Wojtukiewicz MZ, Zacharski LR, Moritz TE, Hur K, Edwards RL & Rickles FR. Prognostic significance of blood coagulation tests in carcinoma of the lung and colon. *Blood Coagulation & Fibrinolysis* 1992; 3(4): 429-437.
11. Buccheri G, Ferrigno D, Ginardi C & Zuliani C. Haemostatic abnormalities in lung cancer: Prognostic implications. European Journal of Cancer 1997; 33(1): 50-55.
12. Seitz R, Rappe N, Kraus M, Immel A, Wolf M, Maasberg M, et al. Activation of coagulation and fibrinolysis in patients with lung cancer: relation to tumour stage and prognosis. Blood Coagulation & Fibrinolysis: An International Journal in Haemostasis and Thrombosis 1993; 4(2): 249-254.
13. Gabazza EC, Taguchi O, Yamakami T, Machishi M, Ibata H & Suzuki S. Evaluating prethrombotic state in lung cancer using molecular markers. Chest 1993; 10(3): 196-200.
14. Brambilla E, Travis WD, Colby TV, Corrin B & Shimosato Y. The new World Health Organization classification of lung tumours. European Respiratory Journal 2001; 18(6): 1059-1068.
15. Detterbeck FC, Boffa DJ & Tanoue LT. The new lung cancer staging system. Chest 2009; 13(6): 260-72.
16. Falanga A. Thrombophilia in cancer. Seminars in Thrombosis and Hemostasis 2005; 3(1): 104-10.
17. Rickles FR & Edwards RL. Activation of blood coagulation in cancer: Trousseau's syndrome revisited. Blood 1983; 62(1): 14-31.
18. Blackwell K, Haroon Z, Broadwater G, Berry D, Harris L, Iglehart JD, et al. Plasma D-dimer levels in operable breast cancer patients correlate with clinical stage and axillary lymph node

status. Journal of Clinical Oncology 2000; 18(3): 600-604

19. Taguchi O, Gabazza EC, Yasui H, Kobayashi T, Yoshida M & Kobayashi H. Prognostic significance of plasma D-dimer levels in patients with lung cancer. Thorax 1997; 52(6): 563-565.
20. Edwards RL, Rickles FR, Moritz TE, et al. Abnormalities of blood coagulation tests in patients with cancer. American Journal of Clinical Pathology 1987; 88(5): 596-602.
21. Bartoloni C, Guidi L, Tricerri A, et al. Latent coagulation disorders evaluated by the assay of plasma thrombin-antithrombin III complexes in a large series of 'Solid Tumours'. Oncology 1992; 49(6): 426-430.
22. Pedersen LM. & Milman N. Prognostic significance of thrombocytosis in patients with primary lung cancer. European Respiratory Journal 1996; 9(9): 1826-1830.
23. Tas F, Kilic L, Serilmez M, Keskin S, Sen F & Duranyildiz D. Clinical and prognostic significance of coagulation assays in lung cancer. Respiratory Medicine 2013; 107(3): 451-457.
24. Yamaguchi T, Yamamoto Y, Yokota S, Nakagawa M, Ito M & Ogura T. Involvement of interleukin-6 in the elevation of plasma fibrinogen levels in lung cancer patients. Japanese Journal of Clinical Oncology 1998; 28(12): 740-744.
25. Meehan KR, Zacharski LR, Moritz TE & Rickles FR. Pretreatment fibrinogen levels are associated with response to chemotherapy in patients with small cell carcinoma of the lung: Department of Veterans Affairs Cooperative Study 188. American Journal of Hematology 1995; 49(2): 143-148.
26. Pavey SJ, Hawson GAT & Marsh NA. Impact of the fibrinolytic enzyme system on prognosis and survival associated with non-small cell lung carcinoma. Blood Coagulation & Fibrinolysis 2001; 12(1): 51-58.
27. Maeda R, Yoshida J, Ishii G, et al. The prognostic impact of cigarette smoking on patients with non-small cell lung cancer. Journal of Thoractomy Oncology 2011; 6(8): 735-742.
28. Owen CAJ, Bowie EJW, Thompson JHJ. The Diagnosis of Bleeding Disorders. Boston: Little, Brown & Company; 1975.
29. Ferrigno D, Buccheri G & Ricca I. Prognostic significance of blood coagulation tests in lung cancer. European Respiratory Journal 2001; 17(4): 667-673.
30. Madoiwa S, Komatsu N, Mimuro J, Kimura K, Matsuda M & Sakata Y. Developmental expression of plasminogen activator inhibitor-1 associated with thrombopoietin-dependent Megakaryocytic differentiation. Blood 1999; 94(2): 475-482.
31. Kuderer NM, Khorana AA, Lyman GH & Francis CW. A meta□analysis and systematic review of the efficacy and safety of anti-coagulants as cancer treatment. Cancer 2007; 110(5): 1149-1161.