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# Is There Any Effect of Tumor Burden on Hemostatic Parameters in Cancer Patients? A Case–Control Study of Hemostatic Abnormalities and Anticardiolipin Antibodies in Solid Tumors

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Hemostatic complications are one of the leading causes of mortality in cancer patients. In the present study, we assessed the hemostatic parameters and anticardiolipin antibodies in patients with solid tumors (n = 104) and healthy controls (n = 25) and also find out whether the abnormalities in these hemostatic parameters vary related to tumor burden. Prothrombin time, activated partial thromboplastine time, D-dimer, and fibrinogen as hemostatic parameters were determined by photo-optometric clot detection system, and serum anticardiolipin levels were measured by enzyme-linked immunosorbent assay. The plasma levels of fibrinogen, D-dimer, and serum anticardiolipin IgM levels in cancer patients were significantly higher compared with those in controls ($P < .001$, $P = .001$, and $P = .01$, respectively). Only fibrinogen levels were significantly higher in metastatic group than nonmetastatic group ($P < .001$ ). Hemostatic abnormalities that are detected in asymptomatic cancer patients may not give any clue about tumor burden or stage of the cancer patients.

**Keywords:** coagulation; cancer; anticardiolipin antibodies; fibrinogen; D-dimer

## Introduction

Abnormalities of hemostatic mechanisms are common in cancer patients. The spectrum of hemostatic abnormalities ranges from massive thromboembolism to abnormal coagulation parameters in the absence of clinical manifestations. Up to 15% of these patients develop clinically evident thromboembolic or bleeding complications. Hemostatic complications are the second most common cause of mortality in cancer patients.[1]

The association between cancer and venous thromboembolism is well known. More than 100 years ago Trousseau reported cases of episodic migratory thrombophelebitis in patients with cancer. Thrombosis may be a presenting feature of occult malignancy, a life-threatening component of early or advanced cancer, or a complication of anticancer therapy itself.

Cancer-related thrombosis represents a complex imbalance between coagulation and fibrinolysis. The underlying pathogenetic mechanisms include hypercoagulability due to activation of clotting by tumor cells, vessel wall injury, and stasis. The activation of coagulation factors V, VII, IX, as well as fibrinogen and fibrin degradation products occurs. Increased secretion of plasminogen activators and decrease in their inhibitors, decreased levels of protein C, protein S, and antithrombin, activation of platelets, and increased platelet aggregation all assist in thrombosis risk. Prolongation of prothrombin time (PT) and activated partial thromboplastine time (aPTT) have also been documented. These changes are thought to be the result of ongoing low-grade disseminated intravascular coagulation (DIC).[1]

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One of the possible contributory causes of thromboembolic disease in cancer is the presence of anticardiolipin antibodies (ACLAs), which may develop secondary to underlying malignancy. Anticardiolipin antibodies may occur in up to 17% of cancer patients and are proposed as one of the contributing factors for hypercoagulability in malignancy. Although it is not known how these antibodies lead to thrombosis, it has been proposed that there is an interaction via altering prostaglandin release, activation of platelets, changes in prostoglandin metabolism or blocking protein C, and altering phospholipid interections with activated factor V. Cancer patients with thrombosis were found to have higher mean levels of IgM ACLAs compared with cancer patients without thrombosis and healthy volunteers.[2]

Some abnormality of hemostasis has been detected in approximately 50% of patients with cancer and in 90% of those with metastatic disease. Clinically evident DIC had been documented in up to 20% of these cases. Most significant changes take place in patients with liver metastasis who are also predisposed to develop thrombotic and hemorrhagic complications.[1]

In our study, we aimed to determine the hemostatic parameters and ACLAs in patients with solid tumors and also examined whether the abnormalities in these hemostatic parameters vary related to tumor burden.

## Materials and Methods

One hundred and four patients diagnosed with various types of cancer were included in the study. There were 59 metastatic and 45 nonmetastatic cancer patients.

Twenty-five healthy individuals without malignancy or thrombosis were enrolled into the study as the control group. The median age of the control group was 54 years (range, 25-74). Patients with infection or collagen diseases and history of thromboembolic events were also excluded in all groups. None of the patients with cancer had indwelling central venous catheters requiring prophylactic anticoagulation. Characteristics of the patients with cancer are summarized in Table 1.

Blood samples were drawn from each group after overnight fasting for measurement of PT, aPTT, plasma D-dimer, plasma fibrinogen and serum anticardiolipin levels. The PT, aPTT, D-dimer, and fibrinogen were measured on the automated BCT analyzer (Dade Behring System, Germany) with photo-optometric clot detection system using Dade Behring kits. Serum anticardiolipin levels were measured by enzyme-linked immunosorbent assay (ELISA) with Genesis kits (Genesis Diagnostics, Cambridgeshire, UK).

**Table 1.** Characteristics of the Patients With Cancer

| | |
|---|---|
| Age (years), median (range) | 53.5 (18-78) |
| Sex | |
| Female | n = 59 |
| Male | n = 45 |
| Cancer type | |
| Breast | n = 25 |
| Gastrointestinal | n = 24 |
| Lung | n = 23 |
| Gynecologic | n = 12 |
| Hematologic | n = 8 |
| Other | n = 12 |
| Stage | |
| Metastatic | n = 59 |
| Nonmetastatic | n = 45 |

The normal ranges of our laboratory for PT and aPTT were 10.4 to 14 seconds and 26 to 40.8 seconds, respectively. The normal levels of fibrinogen were in the range of 180 to 350 mg/dL and for D-dimer in the range of 51 to 285 mg/L. The normal serum anticardiolipin levels were 0 to 10 MPL for anticardiolipin IgM( IgM ACLA) and 0 to 10 GPL for anticardiolipin IgG ( IgG ACLA).

SPSS10.0 for Windows software program was used for statistical analyses. Student's *t* test was used for comparison of the groups.

## Results

The mean plasma levels of fibrinogen, D-dimer, and serum levels of IgM ACLA and IgG ACLA and mean values of PT and aPTT of the patients with cancer and healthy individuals are shown in Table 2.

Mean plasma levels of fibrinogen, D-dimer, and serum IgM ACLA levels were found to be statistically significantly higher in patients with cancer than the mean levels of these parameters in healthy individuals ( $P < .001$, $P = .001$, and $P = .01$, respectively). The PT value was found to be statistically significantly shorter in cancer patients ($P = .043$).

The mean levels of fibrinogen, D-dimer, IgM ACLA, and IgG ACLA and mean values of PT and aPTT of metastatic and nonmetastatic cancer patients are presented in Table 3.

**Table 2.** Mean Levels of Hemostatic Parameters in Cancer Patients and Control Group

| | Fibrinogen (mg/dL) | D-dimer (mg/L) | ACLA IgM (MPL) | ACLA IgG (GPL) | PT (seconds) | aPTT (seconds) |
|---|---|---|---|---|---|---|
| Cancer patients | 484.3 ± 177.1 | 210.7 ± 193.8 | 3.6 ± 3.5 | 5.1 ± 4.4 | 11.9 ± 1.2 | 31.9 ± 7.1 |
| Control group | 270.5 ± 56.22 | 160.2 ± 38.6 | 2.6 ± 2.1 | 2.2 ± 1.5 | 12.4 ± 0.7 | 30.3 ± 2.9 |
| *P* value | <.001[a] | .001[a] | .01[a] | .054 | .043[a] | .397 |

[a]Statistically significant.

**Table 3.** Mean Levels of Hemostatic Parameters in Metastatic and Nonmetastatic Cancer Patients

| | Fibrinogen (mg/dL) | D-dimer (mg/L) | IgM ACLA (MPL) | IgG ACLA (GPL) | PT (seconds) | aPTT (seconds) |
|---|---|---|---|---|---|---|
| Metastatic patients | 530.6 ± 197.2 | 242.3 ± 208.8 | 3.5 ± 3.2 | 4.7 ± 4.3 | 12.2 ± 1.3 | 32.5 ± 8.8 |
| Nonmetastatic patients | 409.9 ± 111.5 | 205.1 ± 221.8 | 3.9 ± 3.9 | 5.6 ± 4.7 | 11.7 ± 0.9 | 31.3 ± 3.9 |
| *P* value | <.001[a] | .918 | .343 | .694 | .144 | .44 |

[a]Statistically significant.

Mean plasma level of fibrinogen was found to be statistically significantly higher in patients with metastatic cancer than the mean plasma levels of patients with nonmetastatic cancer ($P < .001$). There was no difference in the mean plasma levels of D-dimer; serum levels of IgM ACLA and IgG ACLA between metastatic and nonmetastatic cancer patients. Values of PT and aPTT were not found to be similar in the metastatic and nonmetastatic cancer patients.

## Discussion

Hemostatic abnormalities are frequently encountered in patients with cancer. These abnormalities lead to diverse clinical presentations ranging from thrombosis to bleeding or to clinically insignificant abnormal laboratory values. Advanced stage of cancer was found to be a predictor of recurrent venous thrombembolic disease in cancer patients.[3] In this study, we analyzed some hemostatic parameters and ACLAs in cancer patients and compared their levels with those in healthy individuals. We also tried to find out whether the studied parameters change in patients with early and advanced stage cancer.

In our study, the mean plasma levels of fibrinogen and D-dimer were found to be statistically significantly higher in patients with cancer than in healthy individuals. The plasma levels of fibrinogen may reflect a dual situation. Higher values may be an indicator of an acute phase response whereas lower values may be a sign of consumption coagulopathy and the values in between may be the result of combination of these two situations. The mean plasma levels of fibrinogen was also the only studied hemostatic parameter that was found to be statistically higher in metastatic patients than in the nonmetastatic patients.[4]

Higher plasma D-dimer levels were also found to be associated with recurrent thromboembolic disease in cancer patients.[3] In a study by Sagripanti et al,[5] plasma D-dimer levels were found to be higher in metastatic patients compared with those in nonmetastatic patients. In another study[6] plasma D-dimer levels were found to correlate with clinical stage and axillary lymph node status of operable breast cancer patients. Unsal et al[7] have documented statistically higher mean plasma levels of D-dimer in metastatic lung cancer patients compared with nonmetastatic group.

In our study, plasma levels of D-dimer were found to be statistically higher in patients with cancer compared with control group, but no statistically significant difference was detected between the mean plasma levels of metastatic and nonmetastatic cancer patients. Higher levels of D-dimer may indicate a tendency of disseminated intravascular coagulopathy or thrombosis. However, the increase of D-dimer levels was not found to be an indicator of metastatic disease in our study in contrast to some previously published studies. This may partly be because of insufficient number of patients with specific cancer types in our study.

The changes in the measurement of PT and aPTT durations can be considered to have a weak value because there are discrepancies in the measurement of these parameters according to different laboratories and blood sampling methods. Hepatic involvement may affect PT values and the results should be reevaluated considering hepatic or different metastatic sites. In our study, duration of PT was found to be shorter in patients with cancer than in healthy individuals, but this slight difference was not found to be statistically significant between metastatic and nonmetastatic patients. Kies et al[8] have shown that a majority of cancer patients with or without hepatic involvement were able to maintain normal or near normal PT and aPTT levels until advanced stage of disease and deviation from normal for PT and aPTT might signal the presence of a complicating pathophysiologic event such as DIC or cirrhosis.

Anticardiolipin antibodies were shown to be one of the contributing factors to cancer-associated thrombosis. In a previous study at our center, cancer patients with thrombosis were found to have statistically higher mean levels of IgM ACLAs compared with cancer patients without thrombosis and healthy volunteers although the mean values of IgM ACLA were within normal limits.[2]

In our study we also found the mean serum levels of Ig M ACLAs in cancer patients to be statistically higher than the mean levels in the control group and within the normal limits. In a study by Armas et al,[9] serum levels of IgG ACLA were found to be higher in cancer patients compared with the control group and no difference was observed between cancer patients with and without thromboembolic disease. Cancer patients in our study had no history of thrombosis so the higher levels of IgM ACLAs in cancer patients might not be directly related to thrombosis and the cause–effect relationship was not clear. These antibodies were not found be a determinant of advanced metastatic disease in our study. Measurement of serum ACLAs in cancer patients may not reflect a clinically significant abnormality and may not go beyond indicating an otherwise silent laboratory abnormality.

In our study, plasma fibrinogen levels was the only studied hemostatic parameter differing significantly between metastatic and nonmetastatic cancer patients but its role as an acute phase protein might have an impact on this finding. Hemostatic abnormalities that are detected in asymptomatic cancer patients may not give any clue about tumor burden or stage of the cancer patients.

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