Section: General Surgery

Original Research Article

ROLE OF D-DIMER IN PREDICTING NODAL AND HAEMATOGENOUS METASTASIS IN MALIGNANCIES

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Abstract

Background: D-dimer is a fibrin degradation product (or FDP), a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. Fibrinogen is an important source of fibrin, which plays a crucial role in circulating tumour cells extravasation and distant metastasis development. Its stable final product, plasma D-dimer, may be associated with circulating tumour cells appearance and can reflect the metastatic phenotype in cancer patients. The aim and objective of this study is to estimate the D-dimer values in patients with biopsy proven malignant disorders and control population, to compare the D-dimer values between cases and controls and also among the different clinicopathological stages of malignancies. **Materials and Methods:** This is a comparative cross-sectional study done in patients with biopsy proven malignancies admitted to a tertiary care hospital. Tissue diagnosis was made using appropriate modalities based on the location of the tumour. Imaging modalities were carried out to make diagnosis and assess the presence of nodal and haematogenous metastasis and staged and categorized accordingly. Control populations are chosen among surgical patients admitted the in same tertiary care hospital without any known malignancies. Plasma D-dimer was measured for the above patients (both cases and controls) and values collected. D-dimer values were compared between controls and cases and also among the different stages of malignancies. **Result & Conclusion:** In the present study it was demonstrated that plasma D-Dimer levels were high in cancer patients than controls, positively associated with cancer stages, nodal and hematogenous metastasis. These findings suggest that D-dimer level has a potential use in predicting the likelihood of metastasis and progression in various cancers and thus can be used in combination with conventional tumor markers.

INTRODUCTION

Malignancies have become an alarming part of disease load in recent times. The age of incidence has come down from 60 – 70 years in the past to 40 – 50 years in the last 2 to 3 decades. A variety of environmental, personal and lifestyle changes have attributed to this shift. Nodal and haematogenous metastasis are important factors that alter the clinical stages of the malignancies. The intent of treatment is being shifted from curative to palliative with occurrence of metastasis thereby resulting in poor prognosis and this invariably affects the morbidity and survival rate of the patient. [1,2] Most of the patients present themselves to medical centres with advanced stages of malignancies (i.e., with either nodal or haematogenous metastasis) due to lack of awareness and unavailability of modalities to identify the presence of malignancy or metastasis. Even with biopsy proven malignancies many patients end up presenting late due to lack of access or unaffordability to imaging resources. Tumour thrombi formation have been found to be an important step in invasion of malignant tumours and their metastasis (lymphatic or haematogenous).[2] Only after its deposition in distant organs or lymph nodes (seeding) and establishment of tumour microenvironment at that specific organ, the present imaging studies can identify metastasis.

D dimer is the breakdown product of cross-linked fibrin that is formed by activation of the coagulation system. [3,4] Elevated levels of D dimer have been detected in patients with diseases like Disseminated intravascular coagulation, Deep vein thrombosis,

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other thromboembolic diseases, Acute trauma, Recent surgeries, Prolonged immobilization, anti-platelet and anti-coagulant therapy, Chronic inflammatory diseases, vascular occlusion crisis in sickle cell disease, myocardial infarction etc. D dimer is a widely used biomarker for indicating the activation of coagulation and fibrinolysis.[1]

D-Dimer is one marker that is proposed to be a breakdown product of tumour thrombi in vascular channel; thus, its elevated levels prove the presence of circulating tumour cells even before radiological studies could identify them.[5] From previous studies it is known that D-Dimer can be a promising marker in predicting the progression of malignancy,[1] and has an integral part in tumour thrombi formation and its dissemination through vascular channels.

In this present retrospective study, the plasma levels of D dimer in patients with biopsy proven malignancies and healthy controls were compared and association of D-Dimer levels with cancer stages and metastasis were studied in detail.

Aim: To ascertain the role of D- dimer in predicting nodal and hematogenous metastasis in malignancies.

Objectives:

1. To estimate the D-dimer values in patients with biopsy proven malignant disorders and control population under admission.
2. To compare the D-dimer values between patients with biopsy proven malignant disorders and control population.
3. To compare the D-dimer values among the different clinicopathological stages of malignancies.

MATERIALS AND METHODS

Study Type: Comparative cross-sectional study
Study Setting: Tertiary care hospital in South India
Study Population: Patients with biopsy proven malignancies admitted to this tertiary care hospital
Study Period: 1 year, from April 2021 to April 2022
Sample Size: n=56 (in each group); n=112 (in 2 groups)

Inclusion criteria for cases:

Patients more than 18 years of age with biopsy proven malignancies of head and neck, breast, thyroid, abdominal and skin admitted to this tertiary care hospital during the study period and willing to participate in the study.

Exclusion criteria for cases:

Patients with other conditions associated with elevated D-dimer like, Disseminated intravascular coagulation, Deep vein thrombosis, Thromboembolic diseases, Acute trauma, Recent surgeries within 12 weeks, Prolonged immobilization, COVID – 19 positive within 12 weeks, Chronic inflammatory diseases, on anti-platelet and anti-coagulant medications

Patients undergoing cancer chemotherapy either neoadjuvant, adjuvant or palliative chemotherapies

Non-biopsy proven candidates with only suspected malignancies

Patients under 18 years of age and not consenting for the study

Inclusion criteria for controls:

Surgical patients more than 18 years of age with no known malignant disorders admitted to this tertiary care hospital during the study period and willing to participate in the study.

Exclusion criteria for controls:

Patients with other conditions associated with elevated D-dimer like, Disseminated intravascular coagulation, Deep vein thrombosis, Thromboembolic diseases, Acute trauma, Recent surgeries within 12 weeks, Prolonged immobilization, COVID – 19 positives within 12 weeks, Chronic inflammatory diseases, on anti-platelet and anti-coagulant medications

Patients with any history of malignant disorders

Patients under 18 years of age and not consenting for the study

Methodology:

Written and informed consent will be obtained from all the patients before enrollment in the study. This is a comparative cross-sectional study done in patients with biopsy proven malignancies of head and neck, breast, thyroid, abdomen and skin. Tissue diagnosis is made using appropriate modalities like edge biopsy, core needle biopsy, fine needle aspiration cytology, endoscopy or colonoscopy guided biopsy according to the location of the tumour. Imaging modalities like ultrasonogram, computed tomography and magnetic resonance imaging are carried out to make diagnosis and confirm presence of nodal and hematogenous spread. Staging of the tumour was done based on TNM staging and AJCC staging systems and were categorized accordingly. Grading of the tumours obtained from the histopathology reports as reported by pathologists. Control populations are chosen among surgical patients admitted in a tertiary care hospital in South India without any known malignancies. Plasma D-dimer was measured for above patients (both cases and controls) and values collected. The patients in cases group were followed up until the end of study period as to what treatment they underwent and outcome as alive or dead.

D-Dimer Assay: D dimer levels were detected in cancer patients and healthy controls. 2ml whole blood was drawn from the antecubital vein of each subject and collected in 3.2% sodium citrate vacutainer collection tubes. Plasma D dimer levels were analysed with advanced automated random access coagulation analyser (ECL 760). This analyser uses principle of sandwich ELISA and latex enhanced turbidimetric methods to quantify the D-Dimer in the blood.

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RESULTS

In this study done among patients (No. of cases n=56) with biopsy proven malignancies and a control group of surgical patients (No. of controls n=56) with no known malignancies admitted to a tertiary care hospital, mean age of cases and controls were 54.17 and 44.32 respectively and most of the patients falling within 30-60 years of age. Most of the study population were females among cases and males among controls. Out of 56 cases studied, malignancies like basal cell carcinoma, carcinoma anorectum, carcinoma buccal mucosa, carcinoma colon, carcinoma breast, carcinoma lung, carcinoma stomach, carcinoma tongue, hepatocellular carcinoma, papillary carcinoma of thyroid and periampullary carcinoma.

D-Dimer values were highly elevated in patients with proven malignancies when compared with patients in control group (P = 0.000000012) [Table 1]. When D-Dimer levels were compared with cancer stages based on AJCC staging system (Stage I – IV), it was noted to have less significance (P = 0.097). While the same was compared with cancer stages grouped into three categories (mild, moderate and severe) based on severity, there was significant association of D-Dimer levels with increasing cancer stages (P = 0.047) [Fig-1].

When D-Dimer levels were compared with TNM individually, it was noted that significant elevation of D-Dimer levels noted with increasing T stages (P = 0.015), N stages (P = 0.042) and M stages (P = 0.00002). This proves the fact that D-Dimer is significantly associated with tumour size or depth of infiltration, nodal and haematogenous metastasis.

Also, when patients were followed up till the end of study period (about 1 year) and management the patient is undergoing was assessed, it was noted that patients with low levels of D-Dimer went for upfront surgery and those with high levels went for palliative management while patients with medium levels of D-Dimer went for neoadjuvant therapy [Fig-2] and death occurred in 3 patients during the period of study and interestingly all 3 patients had high D-Dimer levels [Fig-3].

Observations from this study show that D-Dimer is an important predictor of tumour progression and can be considered as a marker of prognosis as it is significantly associated with cancer stages (AJCC), TNM staging, nodal and haematogenous metastasis, mode of treatment and even mortality.

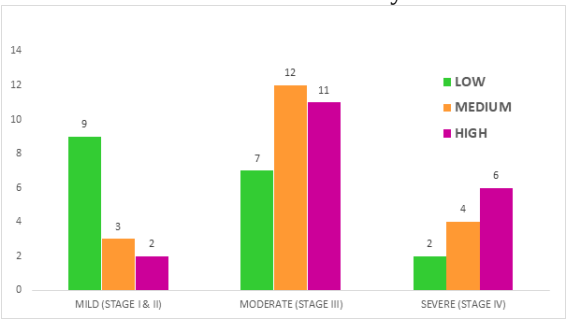

Figure 1: Comparison of D-Dimer values among cancer staging categories

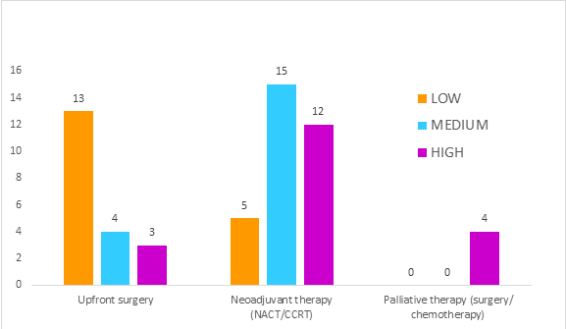

Figure 2: Comparison of cancer management and D-Dimer levels among cases

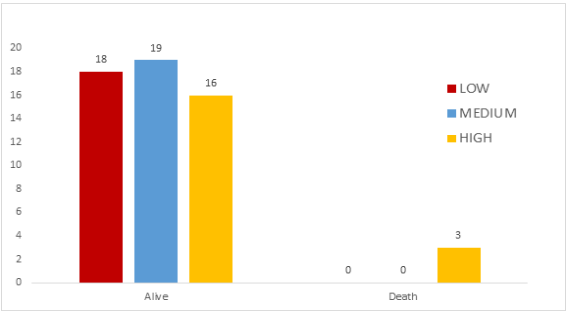

Figure 3: Comparison of patient outcome and D-Dimer levels among cases.

Table 1: Comparison of D-Dimer values among cases and controls

Group	Sample size (n=112)	Negative	Positive
Cases	56	0	56 (100%)
Controls	56	48 (85.71%)	8 (14.28%)
D-Dimer values in cases: Mean ± S.D. = 1380.84 ± 1715.73 D-Dimer values in controls: Mean ± S.D. = 36.86 ± 19.32 P value = 0.000000012			

DISCUSSION

In a study by Diao D et. al. with 41 gastric carcinoma patients, D-dimer increased when Circulating Tumour Cells (CTCs) spread into the vascular compartment which reflects cancer metastasis and might be an accompaniment for Circulating Tumour Cells in gastric carcinoma. They also compared the effectiveness of the levels of D-dimer, Cell Search-CTCs, CEA and Metastasis (as detected by imaging tests and/or by the pathology) and found plasma D-dimer served as a better outcome predictor comparing to Cell Search-CTCs detection, CEA and metastasis in patients with advanced Gastric Carcinoma.[5] Similarly in a study conducted by Blackwell K et. al. among 140 patients undergoing breast biopsies, 102

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were diagnosed with invasive breast carcinoma, 9 with ductal carcinoma-in-situ and 20 with benign breast disease. Plasma D-dimer levels were significantly higher in patients with invasive carcinoma than those patients with either benign breast disease or carcinoma-in-situ. Elevated D-dimer levels predicted positive lymph node involvement and lymph vascular invasion in both univariate regression and multivariate linear regression models. This correlation suggests that detectable fibrin degradation, as measured by plasma D-dimer, is a clinically important marker for lymph vascular invasion and early tumour metastasis in operable breast cancer.[6] In agreement with previous studies cited above, the present study demonstrated that plasma D-Dimer levels were positively associated with nodal and hematogenous metastasis. It is also seen that D-Dimer values also showed significant association with cancer stages, type of management the patient is undergoing and outcome. These findings suggest that D-dimer level has a potential use in predicting the likelihood of metastasis and progression in various cancers. Distant metastasis is the main cause of poor prognosis and leads to inefficacy in treatments in cancer patients. The coagulation/fibrinolytic system is activated in cancer patients and may contribute to cancer progression and plays an important role in cancer metastasis. Thus, tumor-related degradation products of the coagulation and fibrinolytic system have been proposed to predict tumor load and prognosis. Plasma D dimer may reflect the presence of micro-metastases or circulating tumor cells, which may be responsible for tumor recurrence.

CONCLUSION

As D-Dimer levels show positive association with cancer stages, nodal and hematogenous metastasis, it can be used as a predictor of metastasis and prognosis in combination with conventional tumour markers. Its sensitivity and specificity as a sole marker of metastasis and prognosis cannot be stated from above study and thus future investigations are required in this regard.

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