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Coagulation Profile in Neoplastic Conditions: A Prospective Observational Study

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ABSTRACT
Armand Trousseau's 1865 report established the association between cancer and thrombosis. Globally, cancer causes significant mortality, with India reporting 8,08,558 deaths in 2022. Solid organ malignancies exhibit diverse coagulation changes, predisposing individuals to thromboembolic events. This study aims to investigate alterations in haemostatic parameters and their association with cancer. A prospective observational study included 100 cases (60 malignant, 20 benign and 20 healthy controls). Haematological and coagulation parameters, including platelet count, PT, APTT and D-dimer, were assessed. Statistical analysis involved descriptive statistics $\times^2$-test and independent sample t-tests. In malignancies, 73.33% exhibited coagulation abnormalities, with elevated platelet counts, prolonged PT and APTT and 73.33% showing D-dimer levels >200 ng/mL. The study revealed 67.44% compensated, 23.25% overcompensated and 9.30% decompensated ICF in malignancies. Thrombocytosis was observed in 23.25%. Statistical analyses demonstrated significant differences between malignant and benign groups. The study supports the intricate interaction between cancer and the hemostatic system. Elevated D-dimer levels emerged as a universal indicator, reflecting a more aggressive malignant process. Despite the established link between cancer and thrombosis, anticoagulation is not standard, necessitating improved management strategies. Understanding the coagulation profile in cancer aids in predicting and managing complications, emphasizing the importance of assessing D-dimer levels in malignancies.

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Key Words
D-dimer, platelets count, prothrombin time

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INTRODUCTION

In 1865, Armand Trousseau initially reported the correlation between thrombosis and cancer[1]. Globally, cancer stands as a prominent cause of mortality, registering almost 10 million deaths in 2020[2]. In India, as per the National Cancer Registry Programme of the Indian Council of Medical Research (ICMR), cancer contributed to 8,08,558 fatalities in 2022[3]. Malignant diseases exhibit a diverse array of coagulation alterations, creating a proclivity for thromboembolic events or hemorrhage. Such occurrences are notably prevalent in solid organ malignancies, including lung, ovaries, pancreas and mucin-producing gastrointestinal tumors[4].

Spontaneous thrombosis, often arising post-surgery, radiation therapy or anticancer treatment, can serve as an initial indicator of an underlying cancer[5]. In individuals with malignant diseases, the activation of blood coagulation appears to hinge on the release of tumor-derived tissue factors, triggering the extrinsic pathway of the coagulation cascade[6,7]. Evaluating the coagulation profile in cancer provides insights into their association with coagulation abnormalities, aiding in both the anticipation and management of ensuing complications. While previous studies have explored the prognostic implications of coagulation tests for various tumors, the simultaneous occurrence of cancer and coagulation abnormalities remains unexplored. Existing studies on the risk in malignancy patients yield conflicting results[8-10]. Thus, the principal objective of this study is to scrutinize alterations in haemostatic parameters and elucidate their connection to cancer.

MATERIALS AND METHODS:

This prospective investigation, titled "Coagulation Profile in Neoplastic Conditions," was conducted at the Department of Pathology in a tertiary care hospital in Ahmedabad, Gujarat, India, following ethical committee approval from November 2018 to November 2020. The study encompassed a total of 100 cases, comprising 60 cases of malignant lesions, 20 cases of benign lesions and a control group of 20 normal, healthy individuals. Following informed consent, comprehensive patient histories, clinical observations and specific details regarding tumor characteristics were gathered, alongside pertinent laboratory data.

The laboratory Assessments Comprised the Following Procedures:

- **Platelet Count:** Determined using the HORIBA 5-part Automatic cell counter
- **Prothrombin Time (PT):** Assessed with a Fully automatic coagulation analyser-STAGO
- **Activated Partial Thromboplastin Time (APTT):** Examined using a Fully automatic coagulation analyser-STAGO
- **D-Dimer:** Analyzed through the Qualitative latex agglutination test method-TULIP XL FDP kit

To assess haematological parameters, a 2 ml blood sample was collected in an EDTA vacuette and processed using the HORIBA 5-part automatic cell counter for Haemoglobin (Hb), Total count and Platelet count values.

For the assessment of coagulation parameters, a 2 mL blood specimen was procured using a citrate vacuette and subsequently centrifuged at 1500 rpm for 10 minutes at room temperature. The resulting plasma underwent isolation through centrifugation and was then analyzed for Prothrombin time (PT), International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (APTT). D-Dimer analysis employed the qualitative latex coagulation method, utilizing the TULIP XL FDP kit. Plasma extracted from the citrate vacuette served as the sample.

The reference ranges were as follows:

- **Platelet count:** 1,50,000-4,00,000mm³
- **PT (Prothrombin time):** 11-15 sec
- **APTT (Activated Partial Thrombin Time):** 29-35 sec
- **D-Dimer:** Positive = >200ng/mL, Negative = <200ng/mL

Exclusion Criteria Encompassed:

- Patients on heparin or platelet aggregation inhibitors
- Patients with a known primary or secondary bleeding diathesis

A qualitative and semi-qualitative latex slide test was conducted to detect cross-linked fibrin degradation products in human plasma using the TULIP XL FDP kit insert. Owen and Bowie introduced the concept of "intravascular coagulation and fibrinolysis (ICF) syndrome" with the aim of investigating the frequency and nature of haemostatic abnormalities in individuals afflicted with malignancies[11]. Patients were deemed to exhibit intravascular coagulation and fibrinolysis (ICF) if their D-dimer levels exceeded 0.5 µg/dL. The framework proposed by Owen and Bowie for classifying ICF into over-compensated, compensated and de-compensated states was applied, aiming to identify specific tests that could assist in discerning individuals experiencing coagulation-related issues.

The D-dimer and Platelets were used as Indicators and to Separate the Patients into Four Groups:

- Patients with no ICF (normal D-dimer)
- Those with overcompensated ICF (elevated D-dimer and Elevated platelets count)
- Those with compensated ICF (elevated D-dimer but normal platelets count)
- Those with decompensated ICF (elevated D-dimer and decreased platelets count)[12]

This correlation has been linked to acute, subacute and chronic disseminated intra-vascular coagulation (DIC), along with de-compensated, overcompensated and compensated DIC, respectively. A battery of hemostatic tests, including PT, APTT, platelet count and D-dimer, were conducted across these four categories. Notably, the D-dimer test was prioritized in this study for diagnosing intravascular coagulation and fibrinolysis (ICF), as it is currently recognized for its greater specificity in detecting fibrin degradation products, encompassing the formation of FDP, X, Y, D and E fragments derived from either fibrinogen or fibrin during plasma digestion[13,14].

Statistical Analysis: The collected data were inputted into a computerized database for subsequent statistical analysis. Descriptive statistics including mean, standard deviation, standard error of mean, standard error of difference, t-value and 95% confidence intervals were computed for various variables. The x^2-test was employed to evaluate the statistical significance of differences in outcome rates between the two groups.

RESULTS AND DISCUSSION

This study consisted of total 100 cases which include, patients with benign and malignant lesions and normal healthy control. This study is based on qualitative and semi-quantitative D-dimer assay with principle of latex agglutination, along with coagulation profile parameters -PT, APTT and platelet count. Amongst these 100 cases, 60 cases were malignant lesion, 20 were benign and 20 were normal healthy person as a control. In this study we observed that majority of the patients were male (60%), while 40% patients were female. Out of 60 male patients 6 were benign and 40 patients with malignant condition, while 14 were normal healthy person. Out of 40 female patients 14 were benign and 20 patients with malignant condition, while 6 were normal healthy person.

Table 2 outlines lesion distribution, highlighting breast lesions as most prevalent (19%) and kidney lesions as least frequent (3%). Breast lesions, predominantly malignant (57.89%), associated with lymph node metastasis showed D-dimer positive. Liver malignancies, primarily hepatocellular carcinoma (70%) and lung malignancies, mainly non-small cell carcinoma (83.33%), exhibited elevated D-dimer levels. Noteworthy findings include a pancreatic duct adenocarcinoma case with high D-dimer, esophageal squamous cell carcinoma with low D-dimer and mucinous adenocarcinoma of the rectum and colon with elevated D-dimer. Female genital tract and thyroid lesions predominantly showed D-dimer <200 ng/mL, while renal neoplasms and benign soft tissue lesions exhibited low D-dimer. In the control group, all 20 healthy individuals had D-dimer <200 ng/mL.

The present study focused on the altered coagulation profile in neoplastic conditions. Total 100 cases taken, from which 60 cases (60%) were malignant,20 cases (20%) benign and other 20 (20%) were healthy control. Mostly affected age group was >50 years with male predominance (60%). In this study maximum cases (78 cases) were within the range of platelet count <150-400x10^3/mm^3 (Table 3). Malignancies exhibited elevated PT and APTT when compared with control group and benign lesions (Table 3). Out of 60 malignant lesion 44 cases (73.33%) were D-dimer >200 ng/mL (positive) in malignant lesion group. Benign lesion group and healthy control group shows same result of D-dimer with negative result <200 ng/mL (Table 3). In our study, distribution of ICF syndrome cases into compensated, De-compensated and overcompensated ICF in benign and malignant lesion of 100 cases. The majority of patients with malignant lesions with elevated D-dimer showed compensated type of ICF syndrome were 29 cases (67.44%) followed by over-compensated type were 10 cases (23.25%) and

Table 1: Distribution of patients according to their demographic characteristics

Parameters	Number of cases			
Age	Normal	Benign	Malignant	Total
<50 year	20	13	14	47
≥50 year	0	7	46	53
Total	20	20	60	100
Male	14	6	40	60
Female	6	14	20	40
Total	20	20	60	100

Table 2: Distribution of patients according to the site of carcinoma

Site	Frequency	Percentage
Breast	19	19
Lymph node	11	11
Liver	10	10
Lung	12	12
Pancreas	01	01
GIT	07	07
FGT	08	08
Thyroid	05	05
Kidney	03	03
Soft tissue	04	04
Normal healthy control	20	20
Total	100	100

Table 3: Distribution according to Hemogram Profile

Parameters		Number of Cases			
		Normal	Benign	Malignant	Total
Platelet Count					
($X10^3/mm^3$)	<150 X 10^3	0 (0%)	2 (10%)	5 (8.33%)	7
	150- 400 X 10^3	19 (95%)	16 (80%)	43 (71.66%)	78
	>400 X 10^3	1 (5%)	2 (10%)	12 (20%)	15
PT value					
Second)	10-15 Sec.	20 (100%)	19 (95%)	34 (56.66%)	73
	>15 Sec.	0 (0%)	1 (5%)	26 (43.33%)	27
APTT					
(Second)	<29 Sec.	27 (67.5%)	4 (20%)	15 (25%)	46
	29- 35 Sec.	13 (32.5%)	15 (75%)	6 (30%)	34
	>35 Sec.	0 (0%)	1 (5%)	39 (65%)	40
D-dimer	>200 ng/mL (Positive)	0	0	44 (73.33%)	44
	<200 ng/mL (Negative)	20 (20%)	20 (20%)	16 (26.66%)	56
Platelet ($x10^3/mm^3$)					
(ICF syndrome)	150-400 (Compensated)	0	0	29 (67.44%)	29 (67.44%)
	<150 (De-compensated)	0	0	04 (9.30%)	04 (9.30%)
	>400 (Over-compensated)	0	0	10 (23.25%)	10 (23.25%)

Table 4: Statistical comparison between benign and malignant group

Parameters	Malignant	Benign	p-value
PLT	301.65±127.98	268.65±70.45	0.008
PT	15.40±2.60	12.55±0.97	<0.0001
APTT	40.30±10.65	30.71±2.15	<0.0001

Table 5: Statistical comparison between apparently normal control group and malignant group

Parameters	Malignant	Normal	p-value
PLT	301.65±127.98	274.60±47.129	0.007
PT	15.40±2.60	12.25±0.881	<0.0001
APTT	40.30±10.65	29.71±1.855	<0.0001

Table 6: Sensitivity and specificity of qualitative D-dimer test

Parameters	D-dimer Positive (>200 ng mL^{-1})	D-dimer Negative (<200 ng mL^{-1})	Total
Positive samples	44	00	44
Negative samples	00	56	56
Total	44	56	100

de-compensated type were 4 cases (9.30%)(Table 3). Considering all the observations and statistical analysis using independent sample t-test and considering p-value, it was found that all the comparison for above mention variables are statistically significant (Table 4 and 5). This study found 100% specificity and 100% sensitivity of qualitative D-dimer test.

In this study the comparison of PT, APTT with the qualitative result of D-dimer by using independent sample T-test was found statistically significant. (Table 4) show the comparison of PT, APTT measure with malignant and benign lesion group by using independent sample T-test was found statistically significant. p<0.0001. Table-5 show the comparison of PT APTT measure with malignant and healthy control (Normal) group by using independent sample T-test was found statistically significant. p<0.0001. There is no significant difference between the benign lesion group and the healthy control group (p = 0.9). Sensitivity and specificity of qualitative D-dimer test for this study were 100% specificity and 100 % sensitivity.

In this study we studied the hemostatic and coagulation profile in 100 cases (60 showed malignancies, 20 showed benign lesions and 20 were normal group). Complete blood count (for platelet count), PT, APTT, D-dimer, were done. In our study, 73.33% of malignancies exhibited coagulation abnormalities, aligning with findings from studies by Mohammed *et al*. (80%) and Amin *et al*. (88%)[12,15]. Advanced cancer is associated with increased platelet activation, evidenced by elevated platelet turnover and reduced platelet survival time[16]. The mean platelet count in malignancies in our study was 301.65±127.98 × 10^3/cm, higher than in benign lesions (268.65± 70.454 × 10^3/cm) and the normal control group (274.60±47.129 × 10^3/cm). This corresponds with similar studies; for instance, Patel SM *et al*. reported a mean platelet count in malignancies of 334.14±104.56 × 10^3/cm, compared to 273.73±126.52 × 10^3/cm in the control group[17]. Mohammed *et al*., Amin *et al.* and Suega and Bakta also observed elevated mean platelet counts in cancer patients compared to control groups[12,15,19]. However, Omer and Abdalla reported a lower mean platelet count in cancer (249.6±142.3 × 10^3/cm) compared to the control group (279.7±77.9 × 10^3/cm)[18].

In our study, the mean prothrombin time (PT) in malignancies was 15.40±2.608 sec, higher than in benign lesions (12.55±0.973 sec) and normal controls (12.25±0.881 sec). This aligns with findings from Patel *et al*., where malignancies had a mean PT of 23.15±17.48 sec, compared to 14.28±1.91 sec in benign lesions and 13.69±0.89 sec in normal controls[17]. Similar trends were observed by Mohammed *et al*., Amin *et al.* and Omer and Abdalla, indicating higher mean PT values in malignancies compared to control

groups[12,15,18]. For activated partial thromboplastin time (APTT), our study found a mean of 40.30±10.659 sec in malignancies, higher than in benign lesions (30.71±2.153 sec) and normal controls (29.71±1.855 sec). This corresponds with Patel *et al*., reporting a mean APTT of 46.43±18.8 sec in malignancy, compared to 33.66±4.26 sec in benign lesions and 32.95±2.25 sec in normal controls[17]. Significant differences in mean APTT values between the benign and malignancy groups were observed in our study. Mohammed *et al* and Omer and Abdalla also reported higher mean APTT values in cancer patients compared to control groups[12,18].

In 60 malignant cases, 73.33% exhibited elevated D-dimer (>200 ng/mL), indicative of ICF syndrome, whereas benign and control cases showed D-dimer <200 ng/mL. Amin *et al*. reported a mean D-dimer of 3.708±3.236 µg/mL in malignancies compared to 0.325±0.365 µg/mL in controls[15]. Omer and Abdalla observed a mean D-dimer of 2.19632±2.11095 µg/mL in cancer versus 0.21365±0.10357 µg/mL in controls[18]. Mohammed *et al*. noted D-dimer levels of 2-4 µg/mL in cancer and <0.5 µg/mL in controls[12]. Suega and Bakta reported a mean D-dimer of 1.260 µg/mL in malignancies [19]. Patel *et al*. found a mean D-dimer of 2.7246±2.9599 µg/mL in malignancies and 0.3682±0.061 µg/mL in controls[17]. Elevated D-dimer is associated with conditions like DIC, vaso-occlusive crisis, thromboembolic events, myocardial infarction, surgery, inflammation, smoking, senility, pregnancy, trauma and infection. Plasma D-dimer levels correlate with various tumor characteristics and progression factors[19,20].

In our study, 71.66% of malignancy patients exhibited ICF, with 23.25% over-compensated, 67.44% compensated and 9.30% de-compensated ICF. Patel *et al*. reported 88.57% ICF, with 32.26% over-compensated, 61.29% compensated and 6.45% de-compensated ICF[17]. Mohammed *et al*. found 45% ICF, with 38.88% overcompensated, 38.88% compensated and 22.22% de-compensated ICF[12]. Suega and Bakta observed 75.94% ICF, with 40% over-compensated[19]. Omer and Abdalla reported ICF in 88% of patients[18]. In our study, the majority (87%) had normal platelet counts, 10% had thrombocytopenia and 3% had an elevated count, suggesting compensated ICF in most patients, aligning with Omer and Abdalla's findings[18]. In our study, thrombocytosis was observed in 23.25% (n = 10), consistent with Mohammed *et al*.'s findings of 27.5% thrombocytosis in cancer patients [12]. Nagy *et al*. and Dirix *et al*. established a link between elevated D-dimer levels and tumor markers in breast cancer, predicting increased mortality risks, which aligns with our study[21,22]. Similarly, Blackwell *et al*. documented that plasma D-dimer levels correlated with lympho-vascular invasion, clinical stage and lymph node involvement in operable breast cancer, supporting our results[23].

CONCLUSION

Assessing the coagulation profile in cancer can offer insights into complications and aid in prediction and management. Elevated D-dimer levels, observed in our study, may serve as a universal indicator of the intricate relationship between cancer and hemostasis activation, suggesting a more aggressive malignant process with poorer clinical outcomes. The study underscores the multifaceted interaction between malignant cells and the hemostatic system, involving the production of procoagulant and fibrinolytic activities, as well as inflammatory cytokines. Abnormal coagulation activation promotes metastatic spread, tumor growth and survival. Despite the established link between cancer and venous thrombosis, anticoagulation is not standard, prompting the need for better management strategies.

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