The Clinical Utility of Tissue Factor Level as a Biomarker in Multiple Myeloma

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Abstract: Tissue factor is a key component in the initiation of coagulation and may play a role in cancer-related processes such as hypercoagulability, tumor growth, angiogenesis, and metastasis. An early study showed an increased expression of TF in haematologic malignancies as AML, polycythemia vera and essential thrombocythemia. However, the role of TF in MM has not been studied in detail. ***Aim of the work:*** is to assess the clinical utility of tissue factor level as a biomarker for prediction of risk of thromboembolism and its relation to type, stage and duration of disease in multiple myeloma patients. ***Subjects & Methods***: This study included 75 MM patients ***(group I)*** 52 males and 23 females with a mean age of 56.40 ± 5.75 years and 20 age and sex- matched healthy subjects served as controls ***(group II).*** All patients were subjected to detailed clinical examination and investigations which included CBC, liver & kidney functions tests, uric acid, serum calcium, CRP, serum protein electrophoresis, immunofixation,bone marrow aspirate and biopsy, B_2 microglobulin,serum albumin, PT, aPTT, D-dimmer, FDP_S, fibrinogen, tissue factor levels, skeletal survey and bilateral lower limb venous duplex. ***Results*** tissue factor was significantly higher in MM patients than controls (*p*-value 0.0001). there is no statistically significant difference between MM patients when classified according to sex (***P***= 0.3), type of myeloma wither IgG or IgA (***P***= 0.7), and wither were recently diagnosed or already on treatment (***P***=0.7).TF levels were significantly higher in patients expressing Lambda compared with those expressing Kappa chain(***P***= 0.04). IT was higher in patients complicated with DVT than those without DVT (***P***= 0.0001). No difference was reported in patients with or without ischemic CVS (***P***= 0.8). TF levels were higher in patients with positive markers of activated coagulation (D-dimer and FDPs) when compared to those with negative markers (***P***= 0.0001 & 0.002 respectively). TF was positively correlated with D-dimer and FDP (***r*** 0.4&0.3, ***P***= 0.001&0.004 respectively),while negatively correlated with fibrinogen (***r*** -0.3 & ***P***= 0.01). According to therapeutic regimens, TF level showed no statistically significant difference between patients received VAD-based regimen and those who did not (***P***= 0.9), it was lower in patients received brotezomib-based regimen compared to those who did not (***P***= 0.01) while it was higher in patients received thalidomide-based regimen than those who did not (***P***= 0.004). TF levels were positively correlated with duration of treatment with thalidomide (*r* 0.4, ***P*** =0.001). The sensitivity and specificity of the TF level as a marker of thrombosis in MM patients (as determined by the ROC Curve) were found to be 77.3% & 90% respectively. Positive predictive value of 96.7 and negative predictive value of 51.4 and area under the curve of 0.88 were detected.Tissue factor was found to be significantly higher in stage III patients when compared with stage I & stage II (***P***= 0.0001). Also we reported that TF is positively correlated with stage and duration of the disease (***r*** 0.4, ***P***= 0.0001 & ***r*** 0.5 & ***P***= 0.007 respectively) and B_2microglubulines (***r*** 0.4, ***P***= 0.001), but negatively correlated with albumin (***r*** -0.4, ***P***= 0.0001).***Conclusion*** Multiple myeloma patients express high level of tissue factor especially in cases complicated with thromboembolism, those who have positive markers of activated coagulation and those receiving thalidomide. So TF level can be used as a predictor for risk of thrombosis in multiple myeloma patients, its sensitivity, specificity PPV&NPV are for further evaluation on wider scales. The correlations of TF with stage and duration of disease, albumin & B_2microglubulines are finding that necessitate further work to determine the extent to which targeting and monitoring TF expression may be useful, from a diagnostic, prognostic, and therapeutic standpoint.

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1. Introduction

Tissue factor, a transmembrane glycoprotein present on subendothelial tissue, platelets and leukocytes, is a key component in the initiation of coagulation and may play a role in cancer-related processes such as hypercoagulability (Trousseau syndrome), tumor growth, angiogenesis, and metastasis. Indeed, elevated TF expression by cancer cells and their associated endothelial cells has been reported frequently (1).

Cancer patients have a 4-3 fold higher incidence of thrombotic complications, due to multiple risk factors that are not always related to the disease like immobility, indwelling central venous catheters, extrinsic venous compression by tumor. Among hematologic malignancies, multiple myeloma (MM) confers a high risk of developing such complications, with a VTE rate of nearly 10% (2). Factors that have been suggested as contributory to the risk of thromboembolic events TEE in people with MM include newly diagnosed disease status (3), acquired abnormalities in platelet function(4), clotting factors and the coagulation cascade. Associated inherited factors abnormalities such as Factor V Leiden may add further risk (5, 6).

Introduction of the immunomodulatory derivatives (IMIDs) thalidomide and lenalidomide in the therapeutic armamentarium of MM; associated with rates of VTE reaching values up to 14 to 26%, particularly when dexamethasone or chemotherapy are added. The optimal prophylaxis for patients receiving these antiangiogenetic agents is still a matter of debate (2).

Interestingly, in contrast to individuals with solid tumors in whom thrombosis is a marker of poor prognosis, thrombosis does not impact overall survival in patients with myeloma. This finding suggests that the mechanisms of thrombosis in hematological neoplasms may differ from solid epithelial tumors and that thrombosis in the former may be driven by therapy and not by a procoagulant phenotype of the neoplastic plasma cells. This may also explain why thrombosis in the context of IMID-based therapy may be prevented by the use of prophylactic aspirin (7).

Venous thromboembolism was four-fold more common among patients with high TF-expressing carcinomas (26.5%) than among patients with low TF-expressing carcinomas (5.5%) (8). Its expression increases in several types of non-haematologic malignancies, including glioma, pancreatic cancer, non-small cell lung cancer, colorectal, ovarian, prostatic and breast cancer (9).

An early study showed an increased expression of TF in haematologic malignancies, especially leukaemic blasts in acute myeloid leukaemia and platelet-associated TF microparticle in polycythemia vera and essential thrombocythemia (10).However, the role of TF in MM has not been studied in detail.

In contrast, Negaard *et al.,* demonstrated that the hypercoagulable state in haematologic malignancies was not associated with increased levels of circulating TF antigen or TF mRNA. However, this study population was heterogeneous comprising 93 patients with non-Hodgkin lymphoma (52%), acute myeloid leukaemia (22%), chronic lymphocytic leukaemia (15%) and MM (12%) (11).

Aim of the work

The aim of this study is to assess the clinical utility of tissue factor level as a biomarker for prediction of risk of thromboembolism and its relation to type, stage and duration of disease in multiple myeloma patients.

2. Subjects and Methods

The current study included 75 patients ***(Group I)*** who were diagnosed as MM according to IMWG 2003 revised criteria (12) ; they were admitted in the clinical hematology unit, Kasr El Ainy and New Kasr El Ainy teaching hospitals, faculty of medicine, Cairo University. Twenty age and sex- matched healthy subjects served as a control group ***(Group II)***.Verbal consent was provided by all included subjects.

All enrolled patients were subjected to full medical history, complete clinical examination, and investigations which included complete blood picture (CBC), liver & kidney functions tests, serum uric acid, serum calcium, C-reactive protein, investigation of MM (Serum protein electrophoresis, immunofixation, bone marrow aspirate and biopsy and skeletal survey), parameters of staging ISS (B_2 microglobulin and serum albumin), coagulation profile (Prothrombin time PT& activated partial thromboplastin time aPTT), markers of activated coagulation (D- dimmer, fibrinogen degradation products (FDP_S), fibrinogen level, tissue factor level and assessment for DVT with bilateral lower limb venous duplex.

Serum Tissue Factor level assay:

Peripheral blood samples were collected from patients and controls and immediately placed on ice, centrifuged at 3000 g for 15 min. and stored at −20◦C. Serum concentrations of tissue factor were quantified by commercially available Quantikine ELISA methodology according to the manufacturer's instructions.

Statistical analysis:

Statistical Package of social science (SPSS) version 15.0 was used for analysis of data. Data was summarized as mean, SD and frequency. T-test & Non parametric test (Mann Whitney U test when data was not symmetrically distributed) was used for analysis of 2 quantitative data. One way ANOVA test was used for analysis of more than 2 quantitative data followed by post Hoc test for detection of significance. Pearson's and Spearman (when data was not symmetrically distributed) correlation was done. $\boldsymbol{P} < 0.05$ was considered significant, > 0.05 non significant and > 0.01 highly significant, ***r*** was considered weak if < 0.25, mild if $r \geq 0.25$ - < 0.5, moderate if $r \geq 0.5$ - < 0.75 and strong if $r \geq 0.75$. P-value is consider significant if < 0.05*

Receiver Operating Characteristic (ROC) curve was used to identify the ability of the measured biomarker to distinguish between patients' groups and

to obtain sensitivity, specificity, positive and negative predictive values.

3. Results

This study included 75 MM patients ***(group I)*** and 20 age and sex- matched healthy subjects served as controls ***(group II).*** Their ages ranged from 45 to 68 years with a mean of 56.40 ± 5.75 years. Patients' characteristics are shown in table (1). Table (2) shows the laboratory data of ***(group I)***, Table (3) shows comparison between patients and controls regarding TF assay, table (4) shows TF levels in MM patients classified according to their characteristics, Table (5) shows Correlations of TF with clinical & laboratory data, Table (6) shows ROC curve for detection of sensitivity, specificity, positive predictive value and negative predictive value of TF

Table 1; The characteristics of MM patients(*Group I*)

Patients characteristics(no75)	
Age (years)	58.49 ± 6.78 (40-73)
Sex	52(69.3%) Males: 23(30.7%) Females
Disease duration (ms)	8.03±4.35
Type of myeloma	65(86.7%) IgG myeloma: 10(13.3%) IgA myeloma
Type of light chain	39(52%) Lambda: 36(48%) Kappa
Skeletal survey -Normal -Osteolytic lesion -Pathologic collapse -Osteopenia	 15(20%) 35(46.6%) 10(13.3%) 15(20%)
Stage of disease -Stage-1 -Stage-2 -Stage -3	 22(29.3%) 15(20%) 38(50.7%)
Therapy -No(recently diagnosed): On treatment -VAD -Bortezomib -Thalidomide	 46 (61.3%): 29 (38.7%) 11(14.6%) 12(16%) 06(8%)
Thrombotic events -DVT -Ischemic CVS	 18(24%) 15(20.3%)

Table (2): Laboratory data of patients included in the study

Variables	Mean±SD	Variables	Mean±SD
Hb (g/dl)	8.02±0.94	Total protein (g/dl)	10.23±1.44
WBC x 10^3	5.64±2.84	Albumin (g/dl)	2.94±0.66
Platelets x 10^6	172.36±101.40	CRP (mg/dl)	13.05±11.30
Total bilirubin (mg/dl)	1.05±0.61	B_2M (µg/dl)	7580.14±5584.91
Direct bilirubin (mg/dl)	0.36±0.41	PT (sec)	14.94±1.63
AST (IU/L)	29.99±14.78	APTT (sec)	38.96±6.89
ALT (IU/L)	31.51±13.87	Fibrinogen (mg/dl)	3.90±1.45
TF (pg/ml)	69.85±35.11	BMA (% of plasma cell)	42.79±14.46

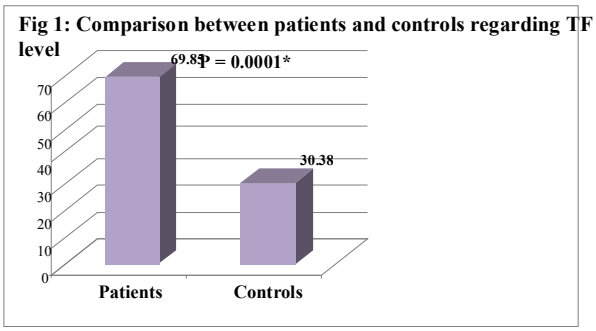
Table (3); Comparison between patients and controls regarding TF assay

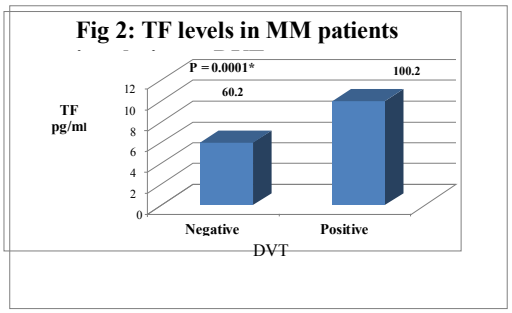
	Patients	Controls	*P*-value
TF (pg/ml)	69.85±35.11	30.38±7.91	0.0001*

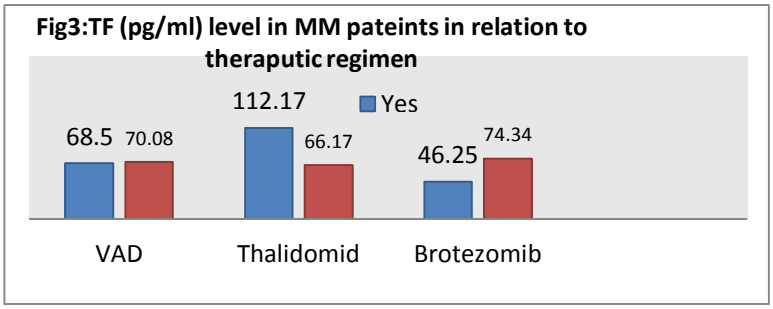
Table (4); Comparing TF levels (pg/ml) in MM patients classified according to their characteristics

Variable	MM Patients (Group I)		P.value		
Sex	Males 67.28±35.42	Females 75.65±34.47	0.3		
Type of Myeloma	IgA Myeloma 65.24±29.10	IgG Myeloma 70.56±36.09	0.7		
Type of light chain	Lambda 75.81±33.56	Kappa 63.39±36.08	0.04*		
Stage of disease	Stage I 54.42±31.87 a		Stage II 51.59±27.7 8 a	Stage III 85.99±32.45 b	0.0001*
Thrombotic events -DVT -Ischemic CVS	Positive 100.26±36.21 66.79±34.01		Negative 60.25±28.98 70.47±35.91	 0.0001* 0.8	
Markers of activated coagulation -FDPs	Positive 74.89±35.37		Negative 43.40±18.29	 0.002*	

-D-dimer	75.74±35.00	41.75±18.49	0.0001*
Therapy	No (recent diagnosis)	On treatment	
	71.53±36.71	67.19±32.87	0.7
Type of medications	Yes	NO	
-VAD	68.50±16.18	70.08±37.50	0.9
-Thalidomid	112.17±29.10	66.17±33.28	0.004*
- Brotezomib	46.25±22.18	74.34±35.44	0.01*







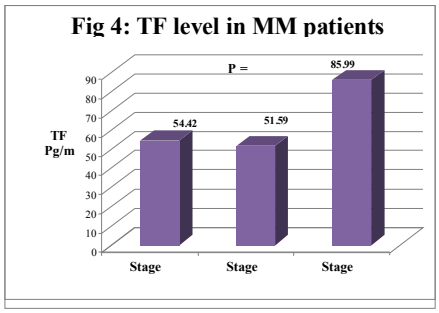


Table (5), Correlations of TF with clinical & laboratory data

Variable	r	*P*-value
D-dimer	0.4	0.001*
FDPs	0.3	0.004*
Fibrinogen (mg/dl)	-0.3	0.01*
Duration of thalidomide ttt	0.4	0.001*
Stage of the disease	0.4	0.0001*
Duration of disease (ms)	0.5	0.007*
Albumin	-0.4	0.0001*
B_2M (µg/dl)	0.4	0.001*

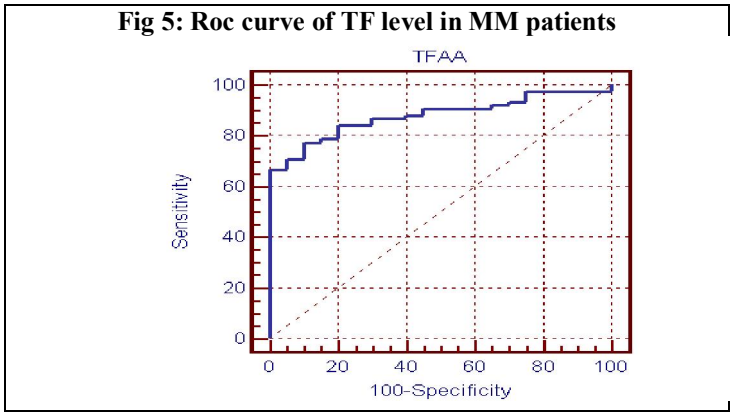


Table (6): Sensitivity, specificity, positive predictive and negative predictive value of TF for risk of thrombosis

Variables	Cut off	Area under the curve	SE	95 % Confidence interval	Sensitivity	Specificity	PPV	NPV
TF	>53.3	0.88	0.04	0.8 – 0.9	77.3	90	96.7	51.4

4. Discussion

The tissue factor-factor VIIa complex is the primary initiator of coagulation *in vivo*. TF appears to play several important roles in cancer including promotion of thrombosis, metastasis, angiogenesis and tumour progression (13.

The diagnosis of multiple myeloma (MM) has been associated to an increased risk of venous thromboembolic events (VTE). Described risk factors that are not exclusive to MM include old age, chemotherapy, immobility, high levels of vascular endothelial growth factor, cancer procoagulant and paraproteinemia. Disease-specific risk factors unique to MM are production of procoagulant autoantibodies, a high incidence of acquired activated protein C resistance, increased levels of factor VIII and von Willebr and factor, and increased production of inflammatory cytokines, mainly IL-6, TNF and C-reactive protein. Treatment regimens that include thalidomide or related compounds such as lenalidomide combined with glucocorticoids and/or cytotoxic chemotherapy were associated with an increased risk of VTE (14).

In the current study we found that, tissue factor was significantly higher in patients with MM than controls (***P***= 0.0001). There is no statistically significant difference between patients when classified according to sex (***P***= 0.3), type of myeloma wither IgG or IgA (***P*** 0.7), and wither patients were recently diagnosed or already on treatment (***P***= 0.7). TF levels were significantly higher in patients expressing Lambda chain when compared to patients expressing Kappa chain(***P***= 0.04).

The finding of high level of TF in MM patients is coincides with a recent study evaluating microparticle associated tissue factor (MP-TF) activity in 123 untreated MM patients demonstrated significantly increased MP-TF activity levels compared to normal volunteers. Although MP-TF activity levels decreased significantly after initiation of chemotherapy on average, they remained persistently elevated in patients who developed VTE during induction chemotherapy **(15).**

Furthermore, Gupta and colleagues studied the expression of TF on archived bone marrow biopsies and plasmacytomas, and human MM cell lines. Immunohistochemical staining of TF was carried out on paraffin-embedded specimens from 18 advanced stage MM patients. TF expression was observed in 10/18 (56%) of the patient specimens. Results from this study suggest that TF is frequently expressed in MM cells and might contribute to the hypercoagulability associated with this disease (16).

In contrary with those findings **Cesarman-Maus *et al.,*** who repeated that F3 (TF gene) was not expressed in 55 human MM cell lines, also F3 expression was absent in tumor samples from 239 MM patients (17)

Notably, the source of increased circulating TF activity in multiple myeloma has not been determined. Several important cytokines and transcription factors that are elevated in patients with MM, such as IL-6, TNF-a, VEGF and NF-jB, are able to increase TF expression on both monocytes and endothelial cells **(18).**

In addition, the regulation of TF by NF-jB p50 is probably important in the pathogenesis of DVT, as inhibition of NF-jB can reduce TF expression and DVT in a mouse models **(18).**

Regarding thrombotic events, we found that TF level was very highly statistically significant higher in patients complicated with DVT than those without DVT (***P***= 0.0001). In contrast, patients complicated with ischemic CVS showed no statistically significant difference regarding TF levels when compared to patients without ischemic CVS (***P***= 0.8)

In many patients with active cancer a systemic activation of the haemostatic and fibrinolytic system is present. Elevated levels of D-dimer and FDPs have been identified to significantly predict risk of VTE in cancer patients **(19)**.

In our study, TF levels were statistically significantly higher in patients with positive markers of activated coagulation (D-dimer and FDPs) when compared to patients with negative markers (***P***= 0.0001&0.002 respectively). Furthermore, we demonstrated a positive correlation between TF and both D-dimer and FDP (***r*** 0.4, ***P***= 0.001 & ***r*** 0.3, ***P***= 0.004 respectively). While a negative correlation was observed between tissue factor and fibrinogen (***r*** -0.3 & ***P***= 0.01).

According to therapeutic regimens, TF level showed no statistically significant difference between patients received VAD-based regimen and those who did not (***P***= 0.9).On the other hand there was statistically significant difference between patients received brotezomib-based regimen and those who did not being lower in patients who received brotezomib (***P***= 0.01).

This coincides with results of **Zangari** who reported that treatment with bortezomib has not been associated with an increased risk of VTE, alone or in combination with dexamethasone and/or chemotherapy.

When bortezomib is given in combination with thalidomide or lenalidomide, the VTE incidence was founded to be low **(20)**. Similar results were reported by **Lonial** *et al.* (21).

This can be explained by the inhibitory effect of bortezomib on platelet aggregation induced by ADP in a dose dependent manner **(22)**. Furthermorem, **Hiroi *et al.*** demonstrated that bortezomib significantly Up-regulate endothelial thrombomodulin expression and enhanced the capacity of endothelial cells to activate protein C **(23).**

There is evidence that the IMDs enhance expression of TF and VEGF, down-regulate thrombospondin, and cause cytokine-mediated, activated protein C resistance **(24)**. Thalidomide has been shown to increase the levels of von Willebrand factor and factor VIII **(25)**. In addition, thalidomide regulates the level of the prothrombotic factor COX-2 and there is some evidence that support an effect on the endothelial cells in patients treated with thalidomide and lenalidomide, possibly via tumor necrosis factor **(26)**. Many authors have reported high incidence of thrombosis with thalidomide with (19, 26, 27).

Our study revealed that there is statistically significantly higher TF level in patients received thalidomide-based regimen than those who did not (***P***= 0.004). Moreover, we found that serum TF levels were positively correlated with duration of treatment with thalidomide (***r*** 0.4, ***P***= 0.001).

The current study showed that, the sensitivity and specificity of the TF level as a marker of thrombosis in MM patients (as determined by the ROC Curve) were found to be 77.3% & 90% respectively. Positive predictive value of 96.7 and negative predictive value of 51.4 and area under the curve of 0.88 were detected.

Concerning tumor progression, it was found that TF is capable of transducing intracellular signals and regulating gene expression (28). Interestingly, elements of the coagulation/fibrinolytic system in general, and TF in particular, have been implicated in regulation of angiogenesis, as well as tumor growth and metastasis in various experimental settings (29). This is consistent with the observed up-regulation of TF in human malignancies and its elevation with advancing disease (30,31) For instance, in human colorectal cancer, TF positivity correlates with clinical stage, histological grade, poor prognosis, and vascularity (32,33). Collectively, these observations suggest that TF is not only an important element of cancer-related coagulopathy but is also a correlate and indeed a likely determinant of malignant behavior of tumor cells.

To our knowledge, no previous research assessed the relation between TF level and progression of myeloma.

In the current study, we found that stage III patients had very highly statistically significant higher TF levels when compared with stage I & stage II patients (***P*** =0.0001). Also we reported a highly significant positive correlation between TF level and stage of disease (***r*** 0.4, ***P***= 0.0001).

A significant positive correlation was observed between tissue factor and duration of the disease (***r*** 0.5 & ***P***= 0.007) was also reported.

On assessment of the relation of TF to variables of International staging system ISS, we found that, TF is positively correlated with B_2microglubulines (***r*** 0.4, ***P***= 0.001). Meanwhile, negatively correlated with albumin (***r*** -0.4, ***P*** =0.0001).

In conclusion, we found that,multiple myeloma patients express high level of tissue factor especially in cases complicated with thromboembolism, those who have positive markers of activated coagulation and those receiving thalidomide, so TF level can be used as a predictor for risk of thrombosis in multiple myeloma patients, its sensitivity, specificity PPV&NPV are for further evaluation on wider scales.

The correlations of TF with stage and duration of disease, albumin & B_2microglubulines are finding that necessitate further work to determine the extent to which targeting and monitoring TF expression may be useful, from a diagnostic, prognostic, and therapeutic standpoint.

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