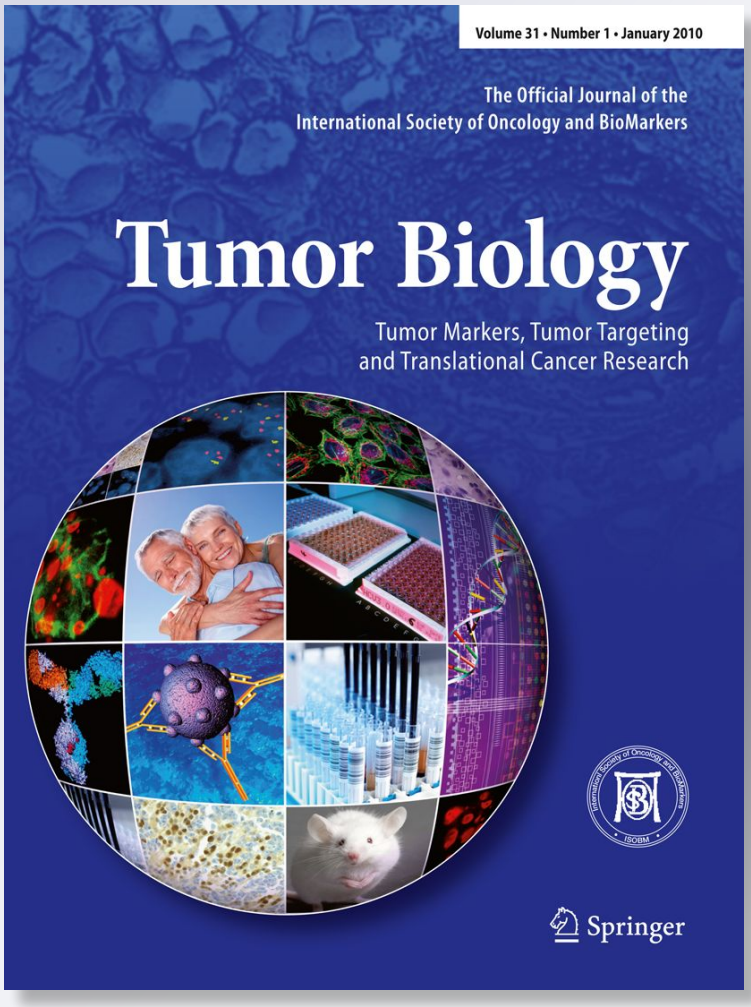
Thrombin activatable fibrinolysis inhibitor and thrombin-antithrombin-III-complex levels in patients with gastric cancer

Evren Fidan, Halil Kavgaci, Asim Orem, Mustafa Yilmaz, Bulent Yildiz, Sami Fidan, Buket Akcan, Feyyaz Ozdemir & Fazil Aydin

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RESEARCH ARTICLE

Thrombin activatable fibrinolysis inhibitor and thrombin-antithrombin-III-complex levels in patients with gastric cancer

Evren Fidan · Halil Kavgaci · Asim Orem · Mustafa Yilmaz · Bulent Yildiz · Sami Fidan · Buket Akcan · Feyyaz Ozdemir · Fazil Aydin

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Abstract The relation between cancer and coagulation is the subject of investigation since a relation between tumor and thrombosis has been determined. Antithrombin III is an important thrombin inhibitor, and increased thrombin–antithrombin (TAT) complex levels activate coagulation. Activated thrombin activatable fibrinolysis inhibitor (TAFI) inhibits the conversion of plasminogen to plasmin. In addition, it directly inactivates plasmin. Defective fibrinolysis increases the risk of thrombosis. In this study, we evaluated homeostatic parameters, TAFI, and TAT levels in patients with gastric cancer applying to the medical oncology outpatient clinic. Fifty-two patients and 35 healthy controls were included. ELISA was used to measure TAFI and TAT complex levels. These were statistically higher in the patient group ($p<0.05$ and $p=0.001$, respectively). D-dimer levels were higher in stage IV ($p=0.05$). Correlations between lymph nodes and TAFI and TAT levels were examined. Weak but positive correlation between lymph nodes and TAFI was detected ($R=0.452$, $p=0.027$). TAFI and TAT levels were evaluated using relative operating characteristic analysis to differentiate the disease. TAT was more specific than TAFI according to this analysis (TAFI area under curve (AUC), 0.676; TAT AUC, 0.874). Thrombotic events and bleeding disorders need to be borne in mind in gastric cancer. This situation is due to the impairment of the balance between coagulation and fibrinolysis. Further studies are now needed to evaluate the effects of TAFI and TAT on survey and prognosis as well as the potential of these parameters as tumor markers for gastric cancer.

Keywords TAFI · Thrombin–antithrombin complex · Gastric cancer

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Introduction

Thrombotic and hemorrhagic complications are the most common cause of death in patients with cancer. Impairment in coagulation may be the first symptom in malignancy [1]. When tumor growth, angiogenesis and end-organ damage develop in patients with cancer; laboratory findings of coagulation activation may also be observed [1]. Anticancer drugs may also accelerate coagulation disorders. Some tumors stimulate coagulation cascade and produce procoagulant substances. These substances produce an inflammatory response, and inflammation affects tumor cells to produce procoagulant substances [2].

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Antithrombin III (AT III) and vitamin K-related coagulation inhibitors try to balance the procoagulant activity. AT III is the most important thrombin inhibitor and causes the formation of irreversible thrombin–antithrombin (TAT) complex. Elevated TAT levels may reveal the activation of coagulation [2]. Thrombin activatable fibrinolysis inhibitor (TAFI) is a glycoprotein synthesized in the liver [3]. Some enzymes, such as trypsin and plasmin, activate TAFI after synthesis. For this activation a considerable amount of thrombin is needed. Activated TAFI inhibits the conversion of plasminogen to plasmin and also directly inhibits plasmin. In these ways, TAFI impairs fibrinolysis [3–5], and impaired fibrinolysis increases the risk of thrombosis in patients with cancer [6, 7].

This study was intended to evaluate TAFI and TAT levels in patients with gastric cancer which is one of the most common cancers in the world. Approximately 989,000 new cases and 738,000 deaths are identified each year worldwide [8]. Patients are generally asymptomatic in the early stages, but by the time it becomes symptomatic, patients are usually in the advanced and incurable phase. Prognosis of gastric cancer is directly related to the stage involved [9, 10]. We investigated whether TAFI and TAT levels are elevated in patients with gastric cancer. Our aim was to evaluate these parameters as markers of coagulation and predicting the disease and to investigate both increased coagulation and decreased fibrinolysis. There are no studies in the literature evaluating these parameters together in gastric cancer patients.

Materials and methods

Patients

Fifty-two patients diagnosed with gastric cancer and 35 controls (age-matched) were enrolled in this case–control trial. The following selection criterion was applied: Chemotherapy naive patients with gastric cancer were enrolled. In addition, exact diagnosis and date of diagnosis were recorded from pathology reports. Patients with renal and hepatic function impairment (creatinine of >1.4 and >1.5 mg/dl for females and males, respectively) (ALT and AST being three times higher than the normal upper limit), class 3–4 coronary insufficiency, chronic inflammatory diseases, those with active infection, pregnant patients and patients using oral contraceptives, and anticoagulants or antiplatelet drugs were excluded. Patients were staged as described in the seventh edition of the American Joint Committee. Blood samples were placed in tubes containing 3.8 % sodium citrate or K_3EDTA as an anticoagulant and serum separator. Plasma and serum supernatants were obtained after the centrifugation of blood samples at 3,000 rpm for 10 min. The remaining serum and plasma samples were kept at −80°C until biochemical analyses.

Routine biochemical parameters were assayed using a Roche Hitachi Cobas 8000 autoanalyzer (Roch, Germany) in a routine setting. CBC was assayed using a Beckman Coulter autoanalyzer in a routine setting.

Table 1 Demographic and clinical characteristics of patients (n=52)

Characteristics	Patients	Controls
Age, mean	57.27±12.90	55.34±16.46
Gender (n)		
Female	31	21
Male	21	14
Lymph node (n)		
1–6	8	
7–15	8	
>15	2	
Disease stage		
IIA	2 (4)	
IIB	5 (10)	
IIIA	7 (14)	
IIIB	5 (10)	
IIIC	9 (18)	
IV	22 (44)	

Table 2 Platelet, PT, PTT, INR, fibrinogen, D-dimer, TAFI, and TAT levels

Parameter	Groups			
	Patient (n=52)	Control (n=35)	Stage IV (n=24)	Stage II+III (n=28)
Platelet (×10^3/ul)	332,959±121,021*	244,228±65,599	329,750±114,101	336,040±129,597
PT (s)	14.57±1.27*	13.11±0.66	14.67±1.49	14.47±1.06
PTT (s)	30.74±3.62	30.06±2.74	31.27±4.34	30.26±2.83
INR	1.15±0.14*	1.06±0.07	1.17±0.18	1.13±0.10
Fibrinogen (mg/dl)	452.50±153.91**	391.35±88.56	495.06±173.59	418.05±130.11
D-dimer (mg/ml)	2.83±3.54*	0.65±0.46	4.3±4.86***	1.64±0.97
TAFI (%)	110.35±32.84**	91.29±23.60	107.77±29.67	112.65±35.83
TAT (ng/ml)	41.31±16.46*	21.32±5.00	40.78±12.46	41.78±19.57

*p=0.0001, compared with the controls

**p<0.05, compared with the controls

***p=0.05, compared with stage II–III patients

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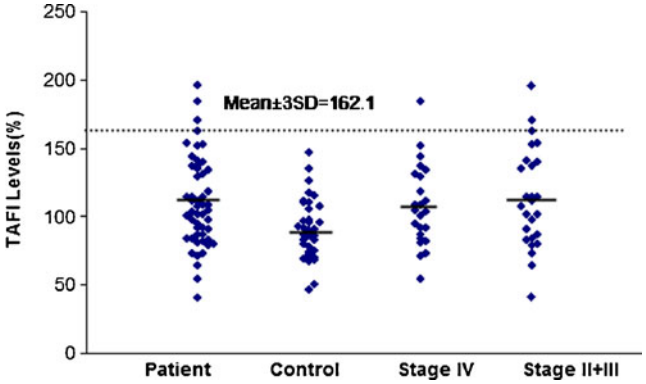


Fig. 1 TAFI levels of patients and controls

D-dimer, PT, PTT, INR, and fibrinogen measurement

D-dimer, prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR), and fibrinogen were assayed using an automatic coagulation analyzer (STA Compact; Diagnostica Stago, Asnieres, France) in a routine setting.

Measurement of TAFI levels

Levels of TAFI were determined using an enzyme-linked immunosorbent assay kit (product no. 873; American Diagnostica Inc., Stamford, USA), according to the manufacturer's instructions. Absorbance of samples was measured at 450 nm using a VERSA max tunable microplate reader (designed by Molecular Devices in CA, USA). The results were expressed as percent.

Measurement of TAT levels

Levels of TAT were determined using an enzyme-linked immunosorbent assay kit (Assaypro, catalog no. ET1020-1; USA), according to the manufacturer's instructions.

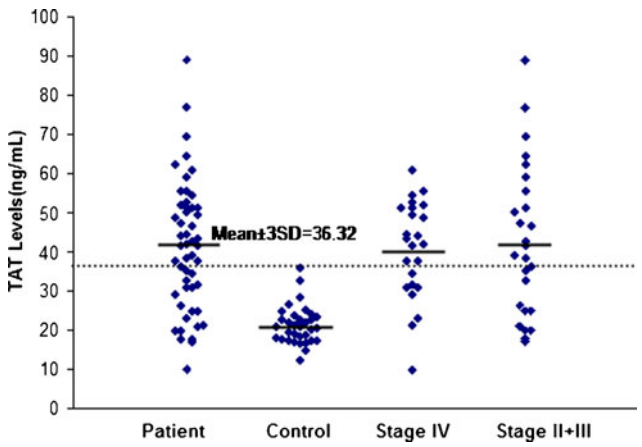


Fig. 2 TAT levels of patients and controls

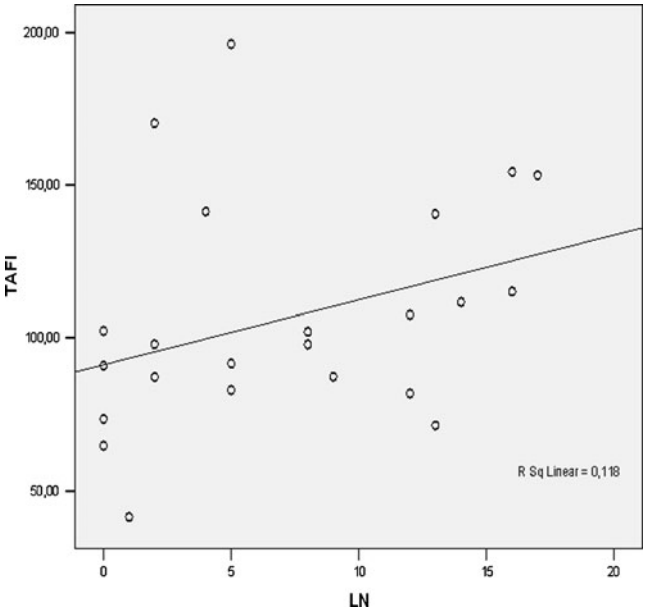


Fig. 3 Correlation graph of TAFI and lymph nodes

Absorbance of samples was measured at 450 nm using a VersaMax tunable microplate reader (designed by Molecular Devices in CA, USA). The results were expressed as nanograms per milliliter.

Statistical analysis

Normality of data distribution was examined using the Kolmogorov–Smirnov test. Differences between the gastric cancer patients and control subjects were investigated using the independent *t* test for data with normal distribution and the Mann–Whitney *U* test for data that did not display a normal distribution. Pearson's correlation coefficient analysis was used to examine the relationship between the parameters. Sensitivity, specificity, negative predictive values (NPV), and positive predictive values (PPV) were calculated according to receiver operating characteristics (ROC) curves. Survival probabilities were estimated using the Kaplan–Meier method. Statistical significance was assumed at a level of $p<0.05$.

Results

Fifty-two patients with gastric adenocarcinoma and 35 controls were included in this trial. There was no statistically significant difference between the patients and the control group in terms of age ($p=0.544$). Only twenty-four patients had metastasis. Nonmetastatic patients were classified into stages among themselves. Blood samples were collected from all patients before chemotherapy; all patients were, therefore, chemotherapy naive.

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Table 3 Separation of patients and controls with ROC analysis

	Cutoff point	Sensitivity (%) (95 % CI)	Specificity (%) (95 % CI)	PPV (%) (95 % CI)	NPV (%) (95 % CI)
TAFI (%)	87.32	72.55 (58.3–84.1)	54.84 (36.0–72.7)	72.5 (58.3–84.1)	54.8 (36.0–72.7)
TAT (ng/ml)	28.59	76.47 (62.5–87.2)	93.55 (78.6–99.2)	95.1 (83.5–99.4)	70.7 (54.5–83.9)

Forty percent (n=21) of the patients were female, and 60 % (n=31), male. Mean age was 57.27±12.90 and 55.34 ±16.46 in the patient and control groups, respectively. Baseline characteristics of patients and controls were recorded (Table 1).

TAFI levels were significantly higher in patients than those in controls (p<0.05). TAT levels were significantly higher in patients, and p value was 0.0001 (shown in Table 2 and Figs. 1 and 2). Patient group's thrombocyte, PT, INR, and fibrinogen levels were significantly higher than those in the control group (p=0.0001, p=0.0001, p=0.0001, and p< 0.05, respectively). When the patient group was analyzed internally, D-dimer levels were higher in the metastatic patients (p=0.0001). Correlations between patients' hemostatic parameters and TAFI and TAT levels were tested, but no negative or positive correlation was determined. We also tested for a correlation between lymph node number and TAFI and TAT levels. A weak but positive correlation was determined between TAFI and lymph node number (R= 0.452; p=0.027), but no correlation was detected between TAT and lymph node number (R=−0.154; p=0.472) (Fig. 3). We also investigated whether TAFI and TAT are parameters that can be used in predicting disease. The sensitivity and specificity of these parameters was evaluated using ROC analysis. TAT level was more specific in predicting disease (Table 3; Figs. 4 and 5). Used to distinguish between metastatic disease stages II and III, their sensitivity was high, but specificity, low. The results are given in Table 4. Patients were monitored for an average of 14 months. In survival analysis, it was detected that patients with TAT levels lower than 32.245 cutoff point are related with short survival. In addition, patients with TAFI levels higher than 108.825 have bad prognosis than others (hazard ratio of 0.919 and 1.010, respectively, and p values of 0.069 and 0.045, respectively; Figs. 6 and 7).

Discussion

The relation between hemostasis and malignity has been investigated in several studies, and thrombolytic complications are more frequent in malign patients. Thrombotic and/or hemorrhagic complications are the most common cause of death in cancer patients [11, 12]. Coagulation defects, which are severe enough to lead to massive thromboembolism and DIC, are seen in patients with malign disease. Abnormal coagulation tests can be seen in 50 % of cancer patients, and around 90 % of these patients have been

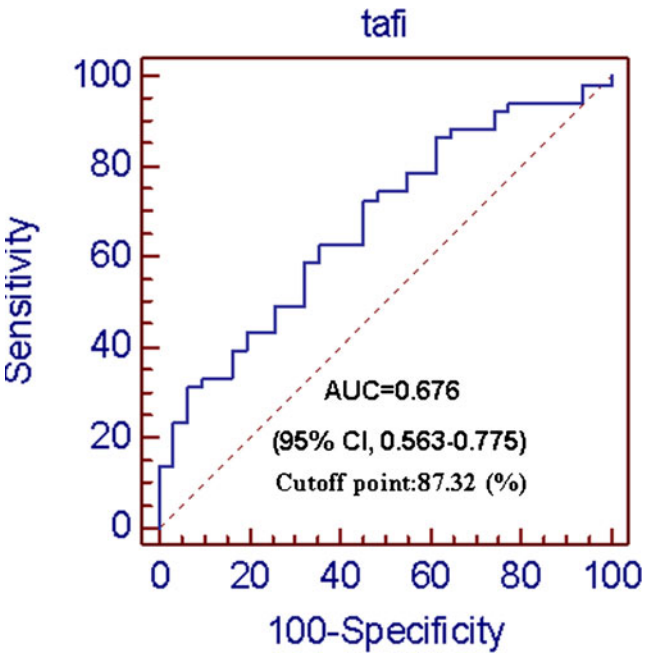


Fig. 4 ROC curve of TAFI for patients and controls

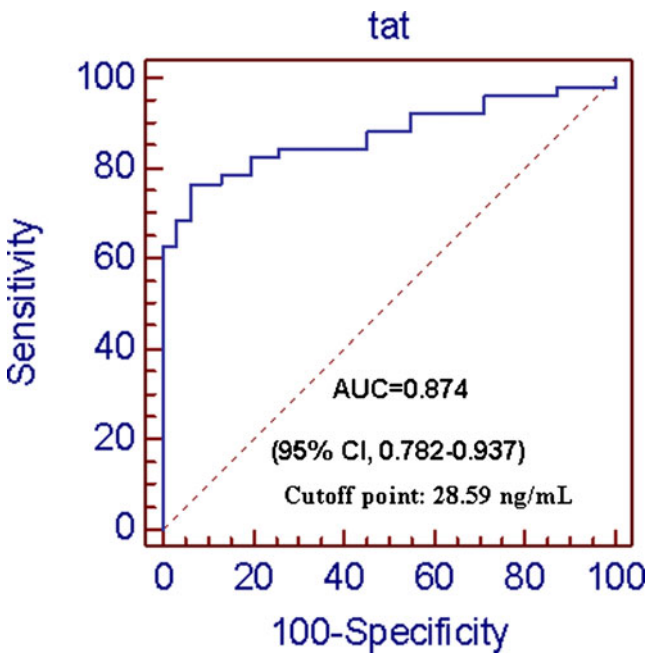


Fig. 5 ROC curve of TAT for patients and controls

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Table 4 Separation of stage IV and stages II–III with ROC analysis

	Cutoff point	Sensitivity (%) (95 % CI)	Specificity (%) (95 % CI)	PPV (%) (95 % CI)	NPV (%) (95 % CI)
TAFI (%)	134.45	83.33 (62.6–95.3)	33.3 (16.5–54.0)	52.6 (35.8–69.0)	69.2 (37.2–91.5)
TAT (ng/ml)	55.34	95.83 (78.9–99.9)	25.93 (11.1–46.3)	53.5 (37.7–68.8)	87.5 (44.0–99.8)

identified in the metastatic period [13–17]. Cancer patients may experience a venous thromboembolism event at a level as high as 15 % at any stage of the disease. Our aim in this study was to investigate hemostasis parameters TAFI and TAT levels in gastric cancer patients. On the basis of previous data, we investigated whether TAFI and TAT levels in gastric cancer patients were parameters demonstrating a predisposition to thrombosis. It has been established in the literature that thrombocytosis is correlated with malign diseases and can lead to poor prognosis in certain forms of cancer [18–20]. Thrombocyte numbers in our study group were statistically significantly higher compared to those in controls. This supports the tendency to thrombosis in patients. PT and INR levels were higher in the patients than in the controls. However, PTT levels exhibited no significant difference. Although there was no difference in PTT values in patients with or without gastric cancer in one study, other studies have determined that prolonged PT is correlated with poorer prognosis [21, 22]. In a study of gastric cancer patients, Kwon et al. [23] determined that PT levels were correlated with lymph node involvement and TNM stage. One coagulation-associated abnormality in cancer patients is increased plasma fibrinogen levels. One study of breast cancer patients determined an increased fibrinogen level compared to the controls. That the same study also determined higher D-dimer levels in the patient group compared to those in the control group [24]. Another study of newly diagnosed breast cancer patients determined elevated D-dimer and fibrinogen. High D-dimer and fibrinogen levels were also reported in a study of 32 breast cancer cases [17, 25]. Fibrinogen and D-dimer levels were also significantly higher in the patient group compared to those in the control group in our study. Tumor growth also activates the fibrinolytic system during angiogenesis and coagulation system activation. Activation of the fibrinolytic system prevents the formation of thrombus in the blood vessels. The end product of the fibrinolytic system is increased D-dimer. The increased fibrinogen and D-dimer levels in our patients show that the fibrinolytic system was activated.

A decrease in coagulation inhibitor production in cancer patients or an increase in the use of these inhibitors may support procoagulant activity. Increased TAT levels suggest coagulation activation [1]. TAT levels in the gastric cancer patients in our study were higher than those in the healthy controls. Pavey et al. [26] determined that TAT levels rose in nonsmall cell lung cancer patients. Ozyilkan et al. [27] reported a similar increase in breast cancer patients. Another study of gastric cancer patients examined plasma TAT levels and determined that these were correlated with lymphovascular invasion [23]. It has been determined that TAT levels rise in approximately 40 % of lung cancer patients and that

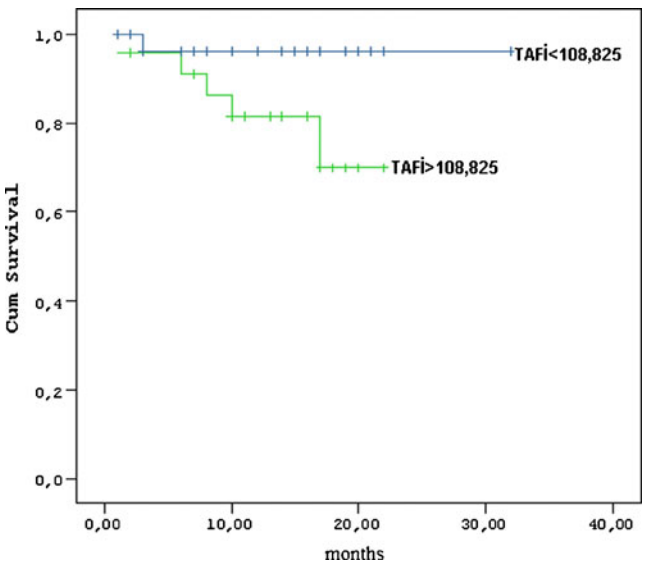


Fig. 6 Kaplan–Meier curves of patients according to TAFI Levels

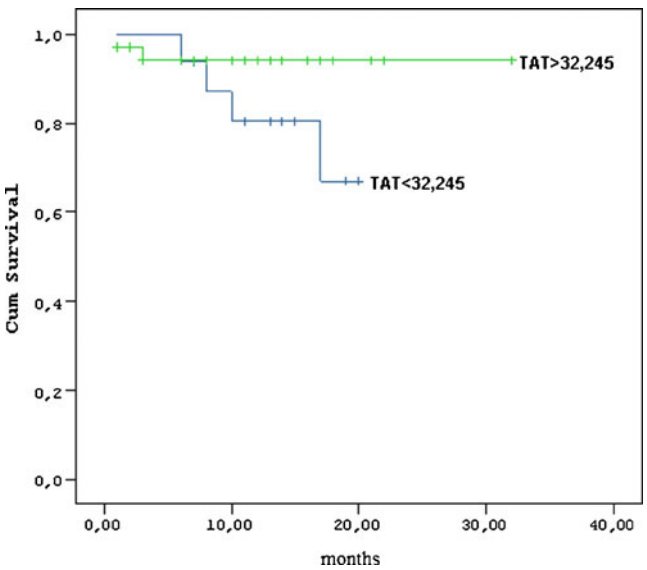


Fig. 7 Kaplan–Meier curves of patients according to TAT Levels

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they are correlated with stage of the disease. This situation has been attributed to the following: It is thought that thrombin actually forms within the tumor tissue and leaks into the circulation with tumor spread, and this accounts for the difference in TAT levels in localized and metastatic patients [28]. We did not observe this difference between metastatic and nonmetastatic patients, but the elevated TAT levels in the patient group show coagulation activation.

The inflammatory cytokines released from cancer cells are thought to increase TAFI manufacture and secretion from liver and/or endothelial cells. Hataji et al. [12] showed that a small cell lung cancer cells series, in particular, can express TAFI mRNA and protein. With systemic activation of the blood coagulation system, TAFI secretion by cancer cells increases intratumor fibrin accumulation and helps the tumor cells to grow and spread [29]. Kaftan et al. [17] determined high TAFI and fibrinogen levels in a study of breast cancer patients. Another study determined lowered TAFI and PAI-1 in acute promyelocytic leukemia patients [30]. We determined higher TAFI levels compared to the healthy controls. (This elevation shows a tendency to thrombus in our patient group).

Our study investigated whether or not TAFI and TAT levels are parameters in disease prediction, and ROC analysis was performed for that purpose. This showed that TAT level was a better parameter in showing disease than TAFI. This study also investigated whether TAFI and TAT levels can be a prognostic marker. Data in the literature show that high TAFI and TAT levels are correlated with poor prognosis [28, 31]. One study of gastric cancer patients determined that tissue factor expression was correlated with poor prognosis, especially in the intestinal type. In another study, plasma prothrombin fragment 1+2, D-dimer, and PT levels were determined to be correlated with lymph gland involvement and stage of disease [23]. A positive correlation has been determined between patients' TAFI level and number of lymph nodes. This means that TAFI rises as lymph node numbers increase, and they also show a poor prognosis. A negative and insignificant correlation was determined between TAT level and lymph node. It is therefore difficult to make a clear interpretation of these data for a correlation between TAT and prognosis. Median length of follow-up for the patients in our study was 14 months. Six of our 52 patients died.

Impaired balance between coagulation and fibrinolysis in gastric cancer patients should be considered, and it should be borne in mind that patients may present with both thrombotic events and also with hemorrhage problems. Heparin procedures are today available for venous thromboembolism treatment and prophylaxis, but it should be borne in mind that only if the target molecules that play a role in coagulation are better understood and identified can specific treatments aimed toward these molecules be developed. The effect of TAFI and TAT levels on gastric cancer prognosis needs to be investigated in longer-term studies with larger patient numbers, and additional studies also need to be designed with regard to whether or not they can be used as tumor markers.

Conflicts of interest None

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