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D-Dimers, Thrombin–Antithrombin Complexes, and Risk Factors for Thromboembolism in Hospitalized Patients

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Introduction There is lack of data about the correlation between hemostatic markers and the clinical and biological risk factors (RFs) for venous thromboembolism (VTE) in medical inpatients without suspicion of acute VTE. **Material and methods** To evaluate the coagulation activation status in patients with current known RFs for VTE, the authors measured 2 markers of hypercoagulability, thrombin antithrombin (TAT) complexes and D-dimers, at day 1 in 165 patients hospitalized in internal medicine wards without suspected acute VTE. All known RFs for VTE were systematically assessed at admission and classified in a chronological way as permanent or transient. **Results** Surprisingly, TAT values followed a multimodal distribution. D-dimers showed a normal distribution after a logarithmic transformation ($P = .34$, Shapiro–Wilk test). Interestingly, a significant progression in D-dimer levels was found according to the chronological classification of RFs. D-dimer variations on multivariate analysis (not applicable for TAT because of the multimodal distribution) correlated independently with a recent inability to walk and an increase in C reactive protein level more than 10 mg/L. **Conclusions** (*a*) this study is the first to describe the variations of hypercoagulability markers according to a systematic screening of RFs for VTE in inpatients without suspicion of acute VTE, (*b*) TAT appeared as a less relevant marker of hypercoagulability than D-dimers in internal medicine inpatients, (*d*) the chronological classification of RFs identified clearly groups at risk for the prethrombotic state, and (*d*) an increased hypercoagulability state was demonstrated in patients with an association between a recent immobility and increased inflammatory markers.

Keywords: thromboembolism; risk factor; hemostatic markers

Introduction

Although numerous studies about hemostatic biomarkers have been performed in patients suspected of deep vein thrombosis (DVT) or pulmonary embolism (PE),[1] no data are available about the level of hemostatic markers according to the risk status for venous thromboembolism (VTE) in nonselected medical inpatients without any suspicion of acute venous thrombosis.

Because they induce venous stasis and inflammatory state, most acute medical diseases are considered as being associated with an increased risk of VTE, though some data suggest that they do not usually lead to a clinical VTE in the absence of chronic intrinsic risk factors (RFs).[2,3] Indeed, in experimental studies a link has been established between systemic inflammation and DVT via an hypercoagulability state resulting from endothelial damage,[4,5] the production of microparticles,[4,6] or a decrease in protein synthesis implicated in the coagulation inhibition phases.[7] Numerous markers for the systemic inflammatory response have been assessed as RFs in clinical studies (ie, C reactive protein [CRP],[8] fibrinogen,[8,9] factor VIII,[10,11] and von Willebrand factor[8]), but

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these studies describe the risk related to a chronic and moderate increase in inflammatory proteins so that the thromboembolic risk because of an acute inflammatory state is not currently known. Moreover, in the medical wards, a nonnegligible number of inpatients have an inflammatory response because of a still undiagnosed progressive disease or diseases not listed in prevention guidelines. Indeed, only infectious, malignant, and rheumatologic diseases are known as being conditions of high risk for VTE.[12]

In the clinical setting, little is known about the real thrombogenic burden of venous stasis even if a deleterious effect can be suspected on the basis of experimental studies.[13,14] In 3 recently published studies testing preventive treatments of VTE in medical inpatients,[15-17] among all the suspected RFs where stasis is expected to play a crucial role, only bed rest and acute respiratory insufficiency appear as selection criteria of patients to receive heparin treatment. However, surprisingly, in patients without acute established VTE or any suspicion of VTE, confinement to bed is currently not a well-demonstrated RF, with results of studies ranging from a clear thrombogenic effect[18] to nonsignificant trends.[19]

The kinetics of thrombin–antithrombin (TAT) complexes has been studied in several animal models of prethrombotic states.[20-22] In the medical setting, TAT variations, D-dimers, and 1 + 2 fragments have been measured in suspected PE[23] in different subgroups of treatment in therapeutic trials[24,25] and in some specific clinical conditions such as pregnancy, diabetes, elderly patients, acute myocardial infarction, and hematological malignancies,[26] but not according to all the thromboembolism RFs in patients without suspicion of VTE.

Our study aims to evaluate the level of D-dimers and TAT according to the presence of clinical RFs for VTE and inflammation markers in patients hospitalized in internal medicine wards.

Materials and Methods

Study Design

This retrospective study is an ancillary project originating from a larger study whose methodology and results have already been reported.[27] It was a monocentric prospective study, performed between January 1995 and November 1997, aimed at describing venous RFs in internal medicine. This study was approved by our local ethics committee. No informed consent was required in the absence of any additive invasive test.

Eligible Patients

All patients hospitalized in a 22-bed unit of internal medicine were eligible, except those who received a high dose of unfractionated heparin or low-molecular-weight heparins (ie, equivalent to the dose recommended for the treatment of DVT) for a suspicion of an ongoing arterial or venous thromboembolic disease.

A clinical screening for signs of DVT and PE was systematically performed by the investigator at admission. All patients with a suspicion for VTE were excluded. Physicians were asked to report all suspicions or confirmed diagnosis of DVT or PE during the hospital stay.

Analysis of Risk Factors

RFs for thromboembolism commonly reported (see Table 1)[28] were assessed by the same investigator on day 1 for each patient included in the initial study. RFs were classified as transient (detected in the last 3 months and still persistent) and permanent (detected more than 3 months earlier). This chronological classification is currently widely accepted.[2,3]

Groups at Risk

According to this classification, 4 groups of patients at risk for thromboembolism could be identified: (*a*) patients with no RFs, (*b*) patients with permanent RFs alone, (*c*) patients with transient RFs alone, and (*d*) patients with permanent and transient RFs.

According to the initial study protocol, in the absence of recommendations for the prevention of VTE in the medical setting at that time, patients have received Nadroparin 0.3 mL a day subcutaneously only if they had transient plus permanent RFs.

Patients Included

To create a plasma bank, 1 of every 5 patients included in the initial study had an additive blood sample at the first day regardless of the group at risk and the underlying condition. We had planned to include 1000 patients in the initial study, so the number of stored samples was expected to be about 200.

Hemostatic Parameters

Venous blood was collected at day 1 and was drawn in plastic syringes containing sodium citrate (0.109 M). Blood samples were centrifuged at 2000*g* for 20 minutes at 4°C. The plasma was carefully removed immediately after centrifugation (5000*g* during 10 minutes), divided into 1-mL aliquots, and stored at −80°C until analysis. Although the stability over time of plasma samples stored at −80°C has been assessed,[29]

Table 1. Classification of Risk Factors for Venous Thromboembolism

Permanent (Detected More Than 3 Months Earlier)	Transient (Detected in the Last 3 Months)
Age more than 60 years	Recent inability to walk[a]
Body mass index >25	Acute cardiac insufficiency
Personal history of unexplained VTE	Dehydration
Chronic inability to walk[a]	Acute inflammatory state[b]
Chronic left cardiac insufficiency	Thrombocytemia >450 000/mm^3
Chronic right cardiac insufficiency	Hematocrit >52%
Progressive malignancy	Puerperium
Estrogenotherapy	Prolonged travel
Pregnancy	
Venous insufficiency	
Varicosis of the lower limbs	
Postphlebitic syndrome	
Congenital thrombophilia	
Lupus anticoagulant	

[a]Bed rest or incapacity to walk around the bed.
[b]Defined by a C reactive protein level ≥10 mg/L or fibrinogen level >4 g/L.

we checked our samples comparing fibrinogen levels measured at day 1 with those measured at the time of the present study (ie, 10 years later). D-dimers and human TAT were measured by enzyme-linked immunosorbent assay commercial kits, as recommended by the manufacturer (D-dimers: Asserachrom D-Di, Diagnostica Stago, Asnieres, France; Human TAT: Enzygnost TAT micro, Dade-Behring, Marburg, Germany). Normal thresholds of D-dimers and TAT were 500 ng/mL and 2 µg/L, respectively.

Inflammatory Parameters

For all the patients included, CRP was measured on venous blood collected in a dry tube at sample collection. CRP determinations were immediately performed in a BNII immunonephelemeter with Dade Behring latex reactives. The CRP normality threshold of our laboratory was 10 mg/L.

Fibrinogen levels (Fibriquick Biomérieux, Lyon, France) were measured at sample collection on venous blood collected in a tube containing sodium citrate (0.109 M). The fibrinogen normality threshold of our laboratory was 4 g/L.

Other Quantitative Data

For blood cells count, blood was drawn by vein puncture into tubes containing ethylenediaminetetraacetic acid and analyzed using an autoanalyzer (XE 2100, Sysmex, Kobe, Japan).

Gammaglobulin screening was performed by capillary electrophoresis (capillarys Sebia). The presence of monoclonal antibody was assessed by immunofixation.

Erythrocyte sedimentation rate (ESR) was obtained by measuring the height of plasma in a dry tube after 1-hour blood sedimentation.

All these tests were done at the time of the initial study.

Statistical Analysis

The normal character of the distributions of the variables TAT and D-dimers (before and after transformation of these variables, if necessary and possible) was tested using the Shapiro–Wilk and Kolmogorov–Smirnov tests with a significant level of 5%.

For univariate analysis, Student's *t* tests when the sample was separated into 2 large enough groups (≥30 individuals per group), Wilcoxon rank-sum tests when the sample was separated into 2 small groups (<30 individuals), and Kruskall–Wallis tests when the sample was separated into more than 2 groups were used to compare means of TAT and D-dimers according to RFs.

Because TAT and D-dimer variables had nonnormal distributions, Spearman coefficients were used to study their correlation with quantitative variables (age, body mass index [BMI], hematocrit, white cells, platelets, CRP, fibrinogen, ESR, and number of permanent and transient RFs for VTE).

For the multivariate analysis, a linear model for log(D-dimers) was obtained by an descending strategy (backward selection). Explicative variables (see Table 2) were age more than 60 years, BMI between 25 and 30 and more than 30, gender, personal history of VTE, chronic and acute inability to walk classified into 3 groups (bed rest, impaired, and normal), progressive malignancy, right or left cardiac failure classified into 3 groups (chronic, acute, or none), dehydration, venous insufficiency, varicosis of the legs, lupus anticoagulant, hematocrit more than 52%, platelets more than 450 000/mm^3, presence of a monoclonal globulin, CRP more than 10 mg/L, fibrinogen more than 4 g/L, leucocytes more than 10 000/mm^3, and ESR more than 15.

Results

Characteristics of the Population

Among the 947 patients included in the initial study, 165 blood samples taken at day 1 were available for measurement of D-dimers and TAT. No DVT or PE has been reported during the hospitalization of these 165 patients.

Table 2. TAT (μg/L) and D-Dimers (ng/mL) According to the Risk Factors for Thromboembolism

			TAT				D-dimers			
Risk factors	Modalities	N	Mean	SD	MED	*P*[a]	Mean	SD	MED	*P*[a]
Age	<60	53	30.5	18	38		1240.5	1547.5	739	
	≥60	112	31.4	17.1	38	0.77	1659.4	1557	1031.5	0.11
BMI	<25	112	29.3	17.9	38		1496.5	1513.6	959	
	[25-30]	38	34.6	16.7	43	0.31	1771.9	1852.4	1117.5	0.41
	≥30	15	33.9	12.6	38		1110.9	989	696	
Gender	Men	75	29.7	18.5	38		1778.9	1829.7	1088	
	Women	90	32.3	16.3	38	0.34	1313.2	1269	933.5	0.05
History of VTE	No	151	31	17.4	38		1541.8	1590.2	964	
	Yes	14	32.4	16.6	38	0.65	1341.6	1244.3	1010	0.95
Walking ability, chronic	Bed rest	39	31.2	17.1	38		1806.2	1662.9	1151	
	Impaired	13	27.2	19.7	38	0.61	1594.5	1445.6	918	0.14
	Normal	113	31.5	17.2	38		1419.7	1539.3	922	
Walking ability, acute	Bed rest	100	32.4	16.7	38		1904.5	1686.9	1197	
	Impaired	21	30.9	17.5	38	0.19	1228.1	1544	759	0.0001
	Normal	44	28.2	18.7	38		928.3	1058.6	619	
Malignancy	History of	15	26.9	19.7	38		2199.5	1847.3	1153	
	None	150	31.5	17.1	38	0.44	1457.4	1520.9	949.5	0.11
Left heart failure	Chronic	29	28.3	18.9	38		1534.2	1350.8	1151	
	Acute	9	37.9	12.3	43	0.68	1856.2	1133.9	1908	0.18
	No	127	31.3	17.2	38		1499.2	1636.6	918	
Right heart failure	Chronic	5	10.8	18	3		1081.4	1031	611	
	Acute	3	27.3	18.5	38	0.02	1773.3	910.2	2185	0.49
	No	157	31.8	17	38		1534.2	1586.9	966	
Dehydration	Yes	9	38.2	13.5	44		2613.8	1392.6	2358	
	No	156	30.7	17.5	38	0.31	1462	1551.6	938	0.005
Venous insufficiency	Yes	52	30.2	18.6	38		1520.2	1261.1	1148.5	
	No	113	31.5	17.1	38	0.63	1527	1687.2	918	0.98
Varicosis	Yes	26	27.9	18.7	38		1388.5	1295	985	
	No	139	31.7	17.1	38	0.51	1550.4	1609.4	964	0.87
Lupus anticoagulant	Yes	2	44	0	44		2267	2371.6	2267	
	No	163	30.9	17.4	38	0.25	1515.7	1557.9	964	0.64
Hematocrit (%)	>52	1	38	—	38		475	—	475	
	≤52	164	31.1	17.4	38	0.77	1531.3	1564.2	965	0.31
White cells (mm^{-3})	<10 000	148	31.4	17.2	38		1444.2	1500.2	949.5	
	≥10 000	16	27.8	18.8	38	0.85	1971.7	1674	1152	0.2
Platelets (mm^{-3})	<450 000	150	30.9	17.3	38		1554.4	1594	974	
	≥450 000	10	34.8	17.3	43.5	0.33	1513.8	1380.1	875	0.98
Monoclonal globulin	Yes	6	31.3	19.7	44		1568.3	1074.8	1491.5	
	No	159	31.1	17.3	38	0.69	1523.2	1579.4	964	0.59
CRP (mg/L)	<10	66	29.2	18.2	38		894.6	997.4	615.5	
	≥10	91	32.5	16.9	43	0.24	1877.2	1649.8	1170	<.0001
Fibrinogen (g/L)	<4	75	28.1	18.2	38		1185	1309	826	
	≥4	67	33.9	16.6	43	0.05	1826.1	1712.3	1170	0.01
ESR (first hour)	<15	36	27.7	18.5	38		793.5	708.6	609.5	
	≥15	98	32.4	17	43	0.17	1667.8	1484.8	1069	0.0009

Abbreviations: TAT, thrombin–antithrombin complexes; MED, median; SD, standard deviation; BMI, body mass index; VTE, venous thromboembolism; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

[a]Student tests for large groups (≥30), Wilcoxon rank-sum tests for small groups (<30), and Kruskall–Wallis tests for more than 2 groups.

Table 3. TAT (μg/L) and D-Dimers (ng/mL) According to the Groups at Risk

		TAT				D-Dimers			
Groups at Risk	N	Mean	SD	MED	*P*[a]	Mean	SD	MED	*P*[a]
No RFs	14	22.8	0.4	23.5		375.4	322.7	279	
Permanent alone	44	29.4	17.7	38		1022.1	1118.1	735	
Transient alone	19	29.7	18.4	38	.049	2021.5	2174.9	1207	.0001
Permanent + transient	88	33.6	16.2	43		1851.9	1575.6	1182	

Abbreviations: TAT, thrombin–antithrombin complexes; SD, standard deviation; MED, median; RF, risk factor.
[a]Kruskall–Wallis test.

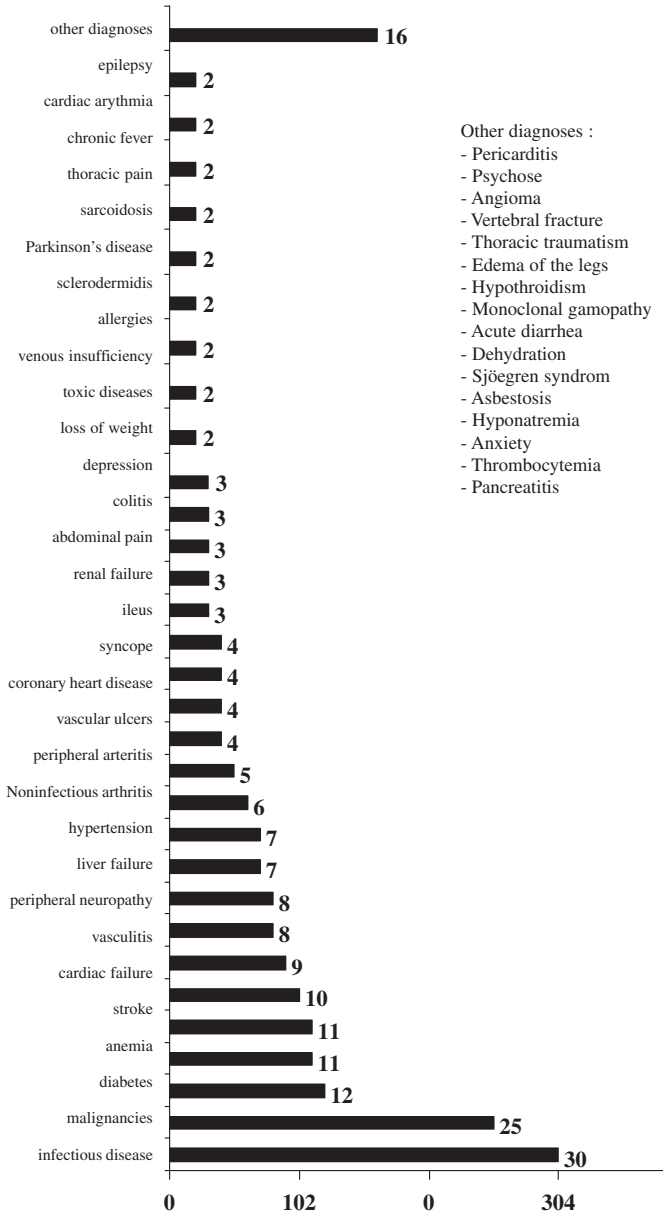

Figure 1. Causes for hospitalization.

The mean age of our population was 71 ± 19 years. On an average, the BMI was 24.1 ± 5.4 kg/m^2. CRP determinations were performed in 157 patients. The median of CRP was 14 mg/L.

The extremely varied reasons for hospitalization (see Figure 1) were representative of internal medicine recruitment. Most of the patients had more than 1 acute disease (on average, 1.4 pathologies per patient).

Distribution of Risk Factors

The distribution of permanent and transient RFs is listed in Tables 2 and 3. More than two thirds (112/165) of the patients included were more than 60 years old. About 10% (15/165) of our cohort were obese. Venous insufficiency and chronic inability to walk were the most frequent venous stasis factors (52/165). A majority of the studied population was recently bedridden (100/165). A total of 57% of the patients included had pathologies responsible for an inflammatory state. Among these patients, about 10% had a progressive malignancy considered here as a permanent RF. A total of 88 patients had permanent and transient RFs, 19 had transient RFs alone, 44 had permanent RFs alone, and 14 had no RFs.

Quality of Storing of Plasma Samples

To evaluate the stability of plasma samples over time, a second determination of fibrinogen levels was performed in October 2007 in 18 patients selected randomly. The mean fibrinogen level for samples taken during the initial study was 5.03 ± 2.63 mg/L compared with 5.09 ± 2.52 mg/L for the second determination ($P = .71$, Student's t test).

Overall Distribution of TAT and D-Dimers

The overall mean of TAT was 31.1 ± 17.3 μg/L, with a median of 38 μg/L. The overall mean of D-dimers

Table 4. TAT and D-Dimers in 165 Patients Hospitalized in Internal Medicine Without Deep Vein Thrombosis

Biomarker	Normal Ranges	Mean	SD	MED	Minimum–Maximum
D-Dimers (ng/mL)	500	1524.8	1561.6	964	112–8960
TAT (μg/L)	2	31.1	17.3	38	2–47

Abbreviations: TAT, thrombin–antithrombin complexes; SD, standard deviation; MED, median.

was 1525 ± 1562 ng/mL, with a median of 964 ng/mL (see Table 4).

The distributions of TAT and D-dimers were nonnormal ($P < .0001$; Shapiro–Wilk and Kolmogorov–Smirnov tests; see Figure 2).

The distribution of TAT was multimodal with a first mode for 2 μg/L, a second for 38 μg/L, and a third for 44 μg/L. We were not able to transform such a variable to obtain a normal distribution.

The distribution of D-dimers was unimodal and was close to a log-normal distribution. After a logarithmic transformation, the transformed variable had a normal distribution ($P = .34$, Shapiro–Wilk test; $P = .46$, Kolmogorov–Smirnov test; see Figure 2).

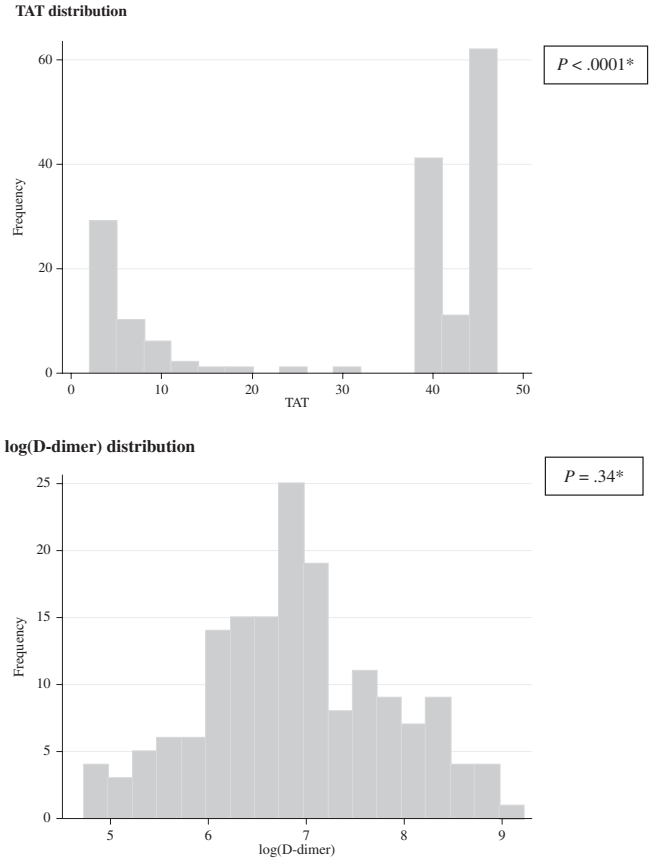

Figure 2. D-dimer and TAT distributions. *Shapiro–Wilk test (null hypothesis: normal variable).

Univariate Analysis According to Risk Factors

Patients with a chronic right ventricular failure seemed protected against elevation of TAT levels (mean TAT = 10.8 μg/L; $P = .02$). Patients with high levels of fibrinogen (>4 g/L) had an increase in TAT levels (mean TAT = 33.9 μg/L; $P = .05$).

TAT was positively correlated with the value of white cells ($r = .22$; $P = .0041$) and CRP ($r = .21$; $P = .0057$).

D-dimer levels were significantly higher in patients with an acute decreased ability to walk, a state of dehydration, an inflammatory state regardless of the marker studied (CRP or fibrinogen), and high ESR (see Table 2).

A positive correlation was found between D-dimers and the age of the patient ($r = .34$; $P < .0001$), white cells ($r = .21$; $P = .007$), CRP ($r = .43$; $P < .0001$), fibrinogen ($r = .18$; $P = .0232$), and ESR ($r = .20$; $P = .001$). A negative correlation was found between D-dimers and hematocrit ($r = -.34$; $P < .0001$).

Univariate Analysis According to the Groups at Risk

There was a positive correlation between TAT and the number of transient RFs ($r = .25$; $P = .0013$) but a nonsignificant correlation between TAT and the number of permanent RFs ($P = .87$). There was a positive correlation between D-dimers and the number of transient RFs ($r = .46$; $P < .0001$) and with the number of permanent RFs ($r = .25$; $P = .0013$).

For TAT, a significant trend was found according to the group at risk for thromboembolism ($P = .049$). Patients with no RFs seemed to have a lower TAT level (22.8 ng/L) than the others (ranging from 29.4 ng/L to 33.6 g/L). A clear significant difference was observed for D-dimers according to the groups at risk ($P = .0001$; see Table 3).

Because log(D-dimers) was distributed according to a normal distribution, an analysis of variance was run on the 4 groups of patients. There was no significant difference between patients with transient RFs alone and patients with transient and permanent RFs ($P = .69$), but the latter group had higher D-dimer levels than patients with permanent RFs alone ($P < .0001$), and patients with permanent RFs alone had higher D-dimer levels than patients with no RFs ($P < .0001$).

Table 5. Final Linear Model for log(D-Dimers) Explained by Risk Factors for Venous Thromboembolism (8 Missing Values)

Log(D-Dimers)	Parameter Estimate	Standard Error	95% Confidence Interval	*P*
Intercept	6.1776	0.1185	5.9435-6.4118	<.001
CRP ≥ 10 mg/L	0.7085	0.1312	0.4493-0.9677	<.001
Recent bed rest	0.4848	0.1321	0.2238-0.7458	<.001
σ^{2a}	0.6391			

[a]σ^2, estimated variance of the residuals.

Multivariate Analysis

A multivariate analysis was not applicable for TAT considering the multimodal distribution of this variable. An analysis after transformation of TAT in a binary variable (TAT inferior or superior to the median) showed the same results as the univariate analysis, that is, only a significant influence of chronic right heart failure.

Among all the accountable factors studied, the independent variables implicated in the elevation of D-dimers were CRP more than 10 mg/L and a recent bed rest (see Table 5):

$$E(\log(\text{D-dimers})) = 6.1776 + 0.7085 \times \text{CRP (more than 10 mg/L)} + 0.4848 \times \text{recent bed rest}$$

According to these results, the level of D-dimers is multiplied by 1.62 for bedridden patients compared with patients with no impaired walking, and the level of D-dimers is multiplied by 2.20 for patients with CRP more than 10 mg/L.

The use of exp[E(log(D-dimers))] as an estimation of the values of the D-dimers for a given patient must be avoided.[30] A correction had been given, multiplying the obtained value by $\exp(\sigma^2/2)$, where σ^2 is the estimated variance of the residuals.[31]

Extrapolating these results, we obtained the following expected mean values of D-dimers:

- 663 ng/mL for patients with a CRP < 10 mg/L and no bed rest ($IC_{95\%}$ = [508;819])
- 1077 ng/mL for patients with a CRP < 10 mg/L and bed rest ($IC_{95\%}$ = [825;1329])
- 1347 ng/mL for patients with a CRP ≥ 10 mg/L and no bed rest ($IC_{95\%}$ = [1023;1671])
- 2187 ng/mL for patients with a CRP ≥ 10 mg/L and bed rest ($IC_{95\%}$ = [1779;2595])

Discussion

TAT and D-dimers are both markers of hypercoagulability. TAT levels are enhanced by the generation of thrombin, and D-dimers, part of fibrin degradation products, are markers of fibrinolysis in response to the activation of coagulation.

These markers have been widely studied in proven[25] or suspected[23] PE or DVT to use them as diagnostic tools. Because a negative value of D-dimers has been demonstrated, it is currently used in clinical practice to rule out PE or DVT.[32] In the present study, these markers have been used in a different goal. Similar to Lopez et al,[26] we have considered them as prethrombotic risk markers in patients without any suspected acute thromboembolism. Although an independent link between increased D-dimer level and risk of DVT has already been demonstrated (odds ratio of about 1.6),[33] the sole objective of this study was to measure the level of coagulation activation according to venous RFs and not to extrapolate our results to a potential clinical thrombogenic effect. From a clinical point of view, D-dimer should only be used as an exclusion tool for DVT. In our internal medicine inpatients, D-dimer levels are increased by a factor of 5 (1525 ng/mL) compared with normal values. Unfortunately, we cannot compare our data with those of Desjardins et al,[24] even though they studied D-dimer variations in the same population (72% of patients had more than 2 RFs in both studies), because they did not use the same method of determination. Lopez et al[26] found an increase by a factor of 14 in acute myocardial infarction and 11 in hematological malignancies (increased by a factor of 11), but in this study also the levels of D-dimers cannot be compared directly because of a different method of determination.

Mean TAT levels (31 ± 17.3 μg/L) were consistent with the published data within a comparable population, that is, medical inpatients with acute pathologies. Indeed, So et al,[34] Lopez et al,[26] and Psuja et al[35] found mean TAT levels of about 23, 38.3, and 59 μg/L, respectively, in patients with rheumatoid arthritis, acute myocardial infarction, and serious infection with the same method of determination. In our study, TAT levels were distributed according to a multimodal distribution, which lowers its interest as a sensitive detection tool for a prethrombotic state compared with D-dimer levels. To our knowledge, no statistical description of TAT distribution is available in medical patients. Lopez et al[26] found a "bimodal-like" repartition of values. Surprisingly, TAT levels were lower in patients with chronic right ventricular failure. Consistent with this result, a protective effect from chronic respiratory failure (frequently associated with right ventricular dysfunction) against DVT was previously noted by Alikhan et al,[12] although the pathophysiological basis of such an effect remains unclear.

Table 3 shows a progression in the level of hypercoagulability according to the chronological classification of RFs. Indeed, patients with permanent RFs had a higher hypercoagulability state than patients with no RFs but a lower hypercoagulability state than patients with transient RFs.

Our study did not demonstrate a synergistic effect of permanent and transient RFs when they are associated. These results were confirmed by analysis of variance. Among the 19 patients with transient RFs alone, 10 had a CRP more than 10 mg/L and 4 had a recent loss of walking. No significant difference in D-dimer levels was found in those subgroups. Nevertheless, these results reinforce the hypothesis of Rosendaal[2] and Cohen et al,[3] suggesting models of thromboembolic risk based on a chronological classification of RFs.

Only 2 independent variables explain the variations of D-dimers: CRP levels and the existence of a recent inability to walk. These results reinforce the current recommendations for prevention of DVT based on the existence of bed confinement, infectious and rheumatologic diseases, and acute respiratory affections.[36] However, taking into account our results, these recommendations could be enlarged by integrating CRP levels instead of inflammatory pathologies and recent inability to walk instead of bed confinement.

This study has some limitations. First, its retrospective nature explains the absence of a systematical screening of confusing factors, such as peripheral arterial disease,[37] stable angina,[38] acute renal failure,[39] and history of acute cerebral ischemia,[40] demonstrated as elevation factors for D-dimer and TAT. Second, despite a clinical screening for VTE at admission, we cannot categorically prove that our patients did not have an acute asymptomatic VTE at admission because no systematic screening by Doppler ultrasound or venography had been performed.

To our knowledge, this study is the first to describe the variations of hypercoagulability markers according to a systematic screening for RFs for VTE at admission in internal medicine units. Three main conclusions can be drawn from this retrospective work: (*a*) TAT appeared as a poorer marker of the prethrombotic state than D-dimers, (*b*) a chronological classification of RFs seems to be relevant in identifying groups at risk for a prethrombotic state, and (*c*) an increased activation of coagulation is demonstrated in patients with a recent inability to walk associated to an inflammatory state and should be confirmed by further prospective studies.

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