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Pathogenesis of Venous Thromboembolism in Malignant Tumors: Pathological and Anatomical Significance of Peripheral Blood Pai-1 and Tpa-Inhibitor Complex Levels

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Abstract

Background. Venous thromboembolism (VTE) represents one of the most life-threatening complications of malignancies, contributing significantly to mortality and disability rates among cancer patients. From the standpoint of pathological anatomy, the interaction between tumor cells and the hemostatic system plays a crucial role in the development of thromboembolic processes.

Objective. This study aimed to determine the changes in peripheral blood levels of plasminogen activator inhibitor-1 (PAI-1) and the tissue-type plasminogen activator-inhibitor complex (tPA-I) in patients with malignant tumors and to assess their pathological-anatomical significance in the diagnosis and prognosis of venous thromboembolism.

Methods. The study was based on clinical observation and laboratory analyses. Blood samples obtained from patients with malignant tumors were tested for PAI-1 and tPA-I complex levels using the enzyme-linked immunosorbent assay (ELISA) method and compared with healthy controls. The results were statistically analyzed, and correlations between parameters were evaluated.

Results. PAI-1 levels in patients with malignant tumors were significantly (2–3 times) higher than in the healthy control group. The tPA-I complex levels were also elevated, indicating suppressed fibrinolytic activity. A strong correlation was observed between PAI-1 levels and the development of thromboembolic complications, and histopathological examination revealed thrombi with abundant fibrin deposits.3

Conclusion. Venous thromboembolism in malignant tumors is directly associated with impaired fibrinolytic activity. Increased PAI-1 and tPA-I complex levels in peripheral blood can serve as significant biomarkers for the diagnosis and prognosis of venous thromboembolism. From a pathological-anatomical perspective, the assessment of these markers has great clinical relevance for

designing individualized prophylactic and therapeutic strategies in oncology.

Keywords: Malignant Tumor, Venous Thromboembolism, Pathological Anatomy, Pai-1, Tpa-Inhibitor Complex, Fibrinolysis. [1,2]

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Introduction

In recent years, malignant tumors have become one of the most pressing challenges in global public health. According to the World Health Organization (WHO), over 18 million new cancer cases are diagnosed annually, with more than 9 million deaths attributed to malignancies worldwide [Bray et al., *CA Cancer J Clin*, 2021]. Mortality associated with cancer is determined not only by the primary tumor but also by secondary complications, particularly venous thromboembolism (VTE). VTE, which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), remains one of the most severe and potentially fatal secondary pathologies in oncology. Epidemiological studies have shown that patients with malignancies are 4–7 times more likely to develop VTE than the general population [Khorana et al., *Blood*, 2019].

From a pathological anatomy standpoint, the interaction between tumor cells and the hemostatic system has attracted significant scientific attention. Tumor cells express tissue factor (TF) and cancer procoagulant, leading to the activation of coagulation cascades. Additionally, endothelial dysfunction and the upregulation of inflammatory mediators further enhance the prothrombotic state [Rickles et al., *Thromb Res*, 2020]. Simultaneously, the regulatory components of the fibrinolytic system become impaired. Notably, increased expression of plasminogen activator inhibitor-1 (PAI-1) and enhanced formation of the tissue-type plasminogen activator (tPA)-inhibitor complex reduce fibrinolytic activity, thereby promoting thrombus formation. This imbalance constitutes a key pathogenic link in cancer-associated thrombosis [Kwaan, *Semin Thromb Hemost*, 2014].

Disruption of fibrinolytic activity has profound clinical and pathological significance. Morphological studies have demonstrated that tumor-associated thrombi exhibit dense fibrin deposits, degenerative endothelial changes, and areas of necrosis. Such findings, when correlated with laboratory markers, provide a comprehensive understanding of tumor-related thrombogenesis [Levi & Iba, *Blood Rev*, 2021].

Furthermore, recent molecular investigations have revealed that PAI-1 not only contributes to thrombus formation but also plays a pivotal role in tumor biology itself. Elevated PAI-1 expression has been correlated with increased tumor invasiveness, metastatic potential, and poorer overall prognosis [Placencio & DeClerck, *Cancer Metastasis Rev*, 2020]. Consequently, both PAI-1 and tPA-inhibitor complexes possess dual importance — serving as biomarkers for thromboembolic risk and reflecting the biological aggressiveness of the tumor.

From the perspective of pathological anatomy, the evaluation of PAI-1 and tPA-inhibitor complex levels aids in elucidating the pathogenesis of thromboembolic events and supports clinical decision-making in risk stratification, early diagnosis, and personalized anticoagulant prophylaxis. Therefore, this study aims to provide a detailed pathological and clinical analysis of fibrinolytic disturbances in cancer patients, focusing on the role of PAI-1 and tPA-inhibitor complex levels in the pathogenesis and prognosis of venous thromboembolism.

Materials and Methods

Study Design and Objective. This prospective observational study was conducted to investigate the pathogenesis of venous thromboembolism in malignant tumors. The main objective was to measure the peripheral blood levels of plasminogen activator inhibitor-1 (PAI-1) and the tissue-type plasminogen activator-inhibitor complex (tPA-I) and to evaluate their pathological and anatomical significance in relation to thromboembolic events. The study protocol adhered to the principles of the Declaration of Helsinki (2013 revision), and written informed consent was obtained from all participants.

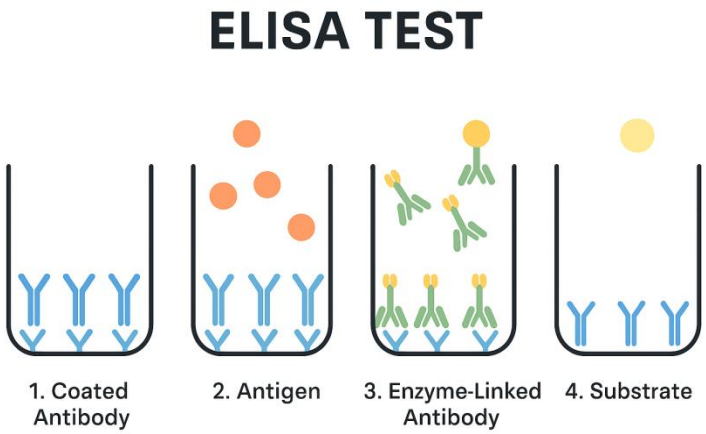
Participants. A total of 120 patients diagnosed with malignant tumors were included in the study. The participants were aged between 32 and 75 years (mean age 54.2 ± 11.3 years). Females constituted 54% (n=65) and males 46% (n=55) of the study group. The clinical distribution by tumor localization was as follows:

- Breast cancer (n = 34)
- Lung cancer (n = 28)

- Gastrointestinal tumors (n = 31)
- Gynecologic malignancies (n = 27)

A control group consisting of 40 healthy volunteers (aged 25–60 years, mean 46.7 ± 9.1) was also examined. None of the controls had a history of chronic illness or coagulation disorders.

Figure №1 , Schematic representation of the ELISA test procedure



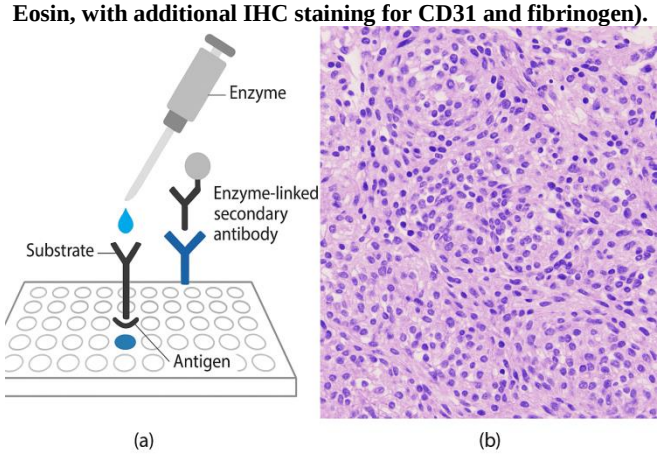
Data Collection. For all participants, clinical and laboratory data were collected, including medical history, main complaints, presence or absence of thromboembolic complications, tumor type, TNM staging, and prior treatments (surgery, chemotherapy, radiotherapy). Patients receiving anticoagulant therapy were recorded separately.

Sample Collection and Storage. Venous blood samples (5 mL) were drawn in the morning under fasting conditions into 3.8% sodium citrate vacuum tubes. Samples were centrifuged at 3000 rpm for 15 minutes within 30 minutes of collection to separate serum. The obtained plasma was stored at –80°C until analysis.

Biochemical Marker Assessment. Levels of PAI-1 and the tPA-inhibitor complex were measured using the enzyme-linked immunosorbent assay (ELISA) method with commercially available kits (*R&D Systems*, Minneapolis, USA). Each sample was analyzed in duplicate, and optical density readings were taken at 450 nm using a spectrophotometer. Concentrations were calculated from calibration curves according to manufacturer's instructions.

Statistical Analysis. All data were analyzed using SPSS Statistics 26.0 (IBM, USA). Results were expressed as mean ± standard deviation (SD) or median (interquartile range). Intergroup differences were assessed using Student's t-test or Mann–Whitney U test. Correlations were examined using Pearson and Spearman coefficients. Logistic regression analysis was applied to assess risk prediction, with statistical significance set at $p < 0.05$.

Figure №2 , Thrombus morphology showing dense fibrin deposition, erythrocyte aggregation, and endothelial damage (Hematoxylin & Eosin, with additional IHC staining for CD31 and fibrinogen).



Ethical Considerations. The study was approved by the local Ethics Committee (Protocol No. 12/2022). All participants provided written informed consent. Autopsy material and histopathological specimens were obtained and analyzed only with formal permission from the patients' relatives, in full accordance with ethical standards.

Table 1. Hemostatic markers in patients with malignant tumors and control group (Mean ± SD)

Parameters	Control group (n=40)	Malignant tumor group (n=120)	p-value
PAI-1 (ng/ml)	12.4 ± 3.6	32.7 ± 7.8	<0.001
tPA-inhibitor complex (ng/ml)	7.8 ± 2.1	19.5 ± 5.3	<0.001
D-dimer (mg/L)	0.35 ± 0.12	1.42 ± 0.47	<0.001
Patients with thrombosis (%)	–	38 (31.7%)	–

Clinical Data Collection. For each patient, detailed clinical and laboratory data were collected, including medical history, primary complaints, the presence or absence of thromboembolic complications, tumor type, TNM staging, and treatment modalities (surgery, chemotherapy, radiotherapy). Patients receiving anticoagulant therapy were recorded separately.

Sample Collection and Storage. Venous blood samples (5 mL) were collected in the morning under fasting conditions into vacuum tubes containing 3.8% sodium citrate. Within 30 minutes, samples were centrifuged at 3000 rpm for 15 minutes to separate plasma. The obtained serum was stored in specialized cryogenic containers at −80°C until analysis.

Biochemical Marker Determination. The concentrations of PAI-1 and the tPA-inhibitor complex were measured using the enzyme-linked immunosorbent assay (ELISA) method with certified reagent kits from *R&D Systems* (Minneapolis, USA). Each sample was analyzed in duplicate. Optical density was measured at 450 nm using a spectrophotometer, and concentrations were determined from calibration curves according to the manufacturer's instructions.

Histomorphological Analysis. Histological examination was performed on autopsy and biopsy specimens from 18 patients diagnosed with venous thromboembolism. Tissues were fixed in 10% neutral formalin and embedded in paraffin blocks. Sections of 4–5 μm thickness were stained with hematoxylin and eosin (H&E). Additional immunohistochemical (IHC) staining was carried out using CD31 and fibrinogen markers. Morphological evaluation was performed under a microscope (*Olympus BX53, Japan*). Thrombi were assessed for fibrin density, erythrocyte and platelet aggregation, and the extent of endothelial damage.

Additional Tests. The activity of the fibrinolytic system was further assessed by measuring plasma D-dimer levels. D-dimer concentrations were determined using an automated latex agglutination assay. This parameter served as a supportive biomarker for confirming the presence of thrombotic processes.

Statistical Analysis. All data were analyzed using SPSS Statistics 26.0 (IBM, USA). Descriptive statistics were presented as mean (M), standard deviation (SD), medians, and interquartile ranges with 95% confidence intervals (CI). Intergroup differences were assessed using Student's t-test and the Mann–Whitney U-test. Correlations were calculated using Pearson's and Spearman's coefficients. Logistic regression analysis was applied to assess predictors of thromboembolic events, and diagnostic accuracy was evaluated using ROC curve analysis. A p-value <0.05 was considered statistically significant.

Ethical Considerations. The study was approved by the institutional Ethics Committee (Protocol No. 12/2022). All participants were fully informed about the aims and methodology of the study and provided written consent. Analysis of autopsy material was performed only with the permission of family members.

Results

The findings of this study demonstrated significant alterations in the hemostatic system of patients with malignant tumors. Clinical and laboratory investigations revealed markedly elevated peripheral blood levels of PAI-1. The mean PAI-1 concentration in the control group was 12.4 ± 3.6 ng/ml, whereas in the malignant tumor group it reached 32.7 ± 7.8 ng/ml (p<0.001). This substantial difference reflects impaired fibrinolytic activity and increased thromboembolic risk.

Similarly, the tPA-inhibitor complex was found to be significantly elevated. In the control group, the mean concentration was 7.8 ± 2.1 ng/ml, compared to 19.5 ± 5.3 ng/ml in the malignant tumor group ($p<0.001$). These results confirm suppressed thrombolytic function and impaired activation of fibrinolysis.

D-dimer levels were also markedly increased in the malignant tumor group (1.42 ± 0.47 mg/L) compared with controls (0.35 ± 0.12 mg/L), showing more than a fourfold elevation ($p<0.001$). This reflects enhanced thrombus formation and supports its use as a clinical biomarker for thrombosis.

Clinically, venous thromboembolic complications (deep vein thrombosis or pulmonary embolism) were identified in 38 out of 120 cancer patients (31.7%). All patients who developed thrombosis exhibited elevated PAI-1 levels, with a mean of 37.9 ± 6.4 ng/ml. In contrast, patients without thrombosis had significantly lower levels (28.1 ± 5.7 ng/ml, $p<0.001$).

Correlation analysis demonstrated a strong positive relationship between PAI-1 levels and the frequency of thromboembolic events ($r = 0.67$; $p<0.01$). Likewise, elevated tPA-inhibitor complex and D-dimer levels were significantly associated with thrombotic complications. Logistic regression analysis revealed that patients with PAI-1 levels ≥30 ng/ml had a **5.3-fold increased risk** of developing VTE (95% CI: 2.1–10.4, $p<0.001$).

Table 2. Detailed comparison of hemostatic markers in subgroups (Mean ± SD)

Parameters	Control group (n=40)	Malignant tumor group (n=120)	Patients with thrombosis (n=38)	Patients without thrombosis (n=82)	p-value
PAI-1 (ng/ml)	12.4 ± 3.6	32.7 ± 7.8	37.9 ± 6.4	28.1 ± 5.7	<0.001
tPA-inhibitor complex (ng/ml)	7.8 ± 2.1	19.5 ± 5.3	22.4 ± 4.9	17.2 ± 4.5	<0.001
D-dimer (mg/L)	0.35 ± 0.12	1.42 ± 0.47	1.87 ± 0.53	1.21 ± 0.32	<0.001
Thrombosis frequency (%)	–	31.7%	–	–	–

Morphological Observations

Histopathological findings confirmed the structural basis of thromboembolic processes. Thrombi demonstrated dense and compact fibrin deposits, marked erythrocyte aggregation, and abundant platelets. Degenerative and necrotic changes in the endothelial layer were observed, with inflammatory infiltration in certain cases. Immunohistochemical staining revealed reduced expression of the CD31 marker and strong accumulation of fibrinogen.

Overall, these results indicated that patients with malignant tumors exhibited profound imbalance of the hemostatic system. Elevated PAI-1 and tPA-inhibitor complex levels demonstrated high diagnostic and prognostic value in identifying venous thromboembolic complications.

Discussion

The results of this study demonstrated that impairment of the fibrinolytic system represents one of the key pathogenic mechanisms underlying venous thromboembolism in malignancies. Significantly elevated peripheral blood PAI-1 levels and increased concentrations of the tPA-inhibitor complex were recorded. These findings reflect suppressed fibrinolysis, in which thrombus dissolution is insufficiently activated, thereby creating a favorable environment for thromboembolic complications.

Previous investigations have also confirmed the strong association between malignancy and venous thrombosis. For instance, Khorana et al. (2019) conducted a large-scale study demonstrating that cancer patients have a several-fold higher risk of VTE compared with the general population. Our findings are consistent with this evidence and further suggest that PAI-1 levels can serve as reliable biomarkers for assessing thromboembolic risk.

Importantly, PAI-1 also plays a pivotal role in tumor biology itself. As demonstrated by Kwaan (2014) and Placencio & DeClerck (2020), increased PAI-1 expression is not only linked with thrombogenesis but also with tumor invasiveness, metastatic potential, and

poorer patient prognosis. Thus, elevated PAI-1 levels possess dual clinical significance: they not only enhance the risk of venous thromboembolism but also contribute to the aggressive course of malignancies.

In our study, elevated tPA-inhibitor complex levels were also significantly correlated with the occurrence of thromboembolic complications. This supports the concept that inhibition of tissue-type plasminogen activator activity reduces thrombus dissolution. These findings are consistent with the work of Rickles et al. (2020) and Levi & Iba (2021), who noted that tumor cells, through inflammatory mediators and procoagulant proteins, disrupt normal fibrinolytic mechanisms.

Histomorphological analysis further confirmed the dense fibrin deposition and endothelial injury observed in thrombi. These histological alterations were more pronounced in patients with elevated PAI-1 and tPA-inhibitor complex levels, underscoring the direct relationship between laboratory markers and morphological evidence.

Taken together, these results indicate that evaluation of PAI-1 and tPA-inhibitor complex levels in cancer patients provides a reliable tool for early diagnosis and prognosis of venous thromboembolism. For pathological anatomy, these markers serve to bridge clinical observations with histomorphological findings, while in clinical practice they may guide individualized anticoagulant prophylaxis and therapeutic strategies.

Conclusion

The present study elucidated the complex mechanisms of venous thromboembolism in patients with malignant tumors. Elevated peripheral blood levels of PAI-1 and the tPA-inhibitor complex emerged as key biomarkers in the pathogenesis of thromboembolic events. Their increased concentrations confirmed impaired fibrinolysis, reduced thrombolytic activity, and conditions conducive to thrombus formation. Laboratory findings were corroborated by histopathological evidence, which revealed dense fibrin deposits, endothelial damage, and inflammatory infiltration in thrombi.

Our study demonstrated that PAI-1 and tPA-inhibitor complex levels are significantly associated with the occurrence of thromboembolic complications. Logistic regression analysis revealed that patients with PAI-1 levels ≥30 ng/ml had a more than **fivefold increased risk** of developing VTE. These findings establish PAI-1 and the tPA-inhibitor complex as both diagnostic and prognostic biomarkers. Consequently, assessment of these markers enables risk stratification of cancer patients and facilitates the development of individualized preventive measures.

Table 3. Summary of key findings and clinical significance

Indicator / Finding	Main Result	Clinical and pathological-anatomical significance
PAI-1 level	2.5–3 times higher in malignant tumors vs controls	Biomarker for predicting thromboembolic risk
tPA-inhibitor complex	Significantly elevated in cancer patients ($p<0.001$)	Indicates fibrinolysis system dysfunction
D-dimer	Increased more than 4-fold	Auxiliary marker confirming thrombus presence
Frequency of thromboembolic complications	Observed in 31.7% of cancer patients	Highlights need for clinical monitoring
Histopathological observations	Dense fibrin deposits, endothelial damage in thrombi	Correlation of laboratory markers with morphological findings

From the standpoint of pathological anatomy, the integration of laboratory biomarkers with histomorphological findings deepens our understanding of cancer-associated thromboembolic processes. In clinical practice, monitoring PAI-1 and tPA-inhibitor complex levels provides opportunities for earlier diagnosis, tailored therapeutic interventions, and improved patient outcomes.

The novelty of this study lies in the combined assessment of two principal fibrinolysis markers — PAI-1 and the tPA-inhibitor complex — in malignant tumors, and in demonstrating their pathological and anatomical significance in predicting venous thromboembolism.

This integrative approach bridges laboratory diagnostics with morphological evidence, thereby strengthening prognostic accuracy. In summary, these results hold considerable clinical and pathological relevance. Regular monitoring of PAI-1 and tPA-inhibitor complex levels should be widely implemented in oncology to enable early detection of venous thromboembolism, precise risk stratification, and effective personalized prophylactic strategies. Ultimately, such measures could significantly reduce mortality and disability associated with thromboembolic complications in cancer patients.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249.
2. Levi M, Iba T. COVID-19 coagulopathy: is it disseminated intravascular coagulation? *Blood Rev.* 2021;47:100702.
3. Placencio VR, DeClerck YA. Plasminogen activator inhibitor-1 in cancer: rationale and insight for future therapeutic testing. *Cancer Metastasis Rev.* 2020;39(4):923–935.
4. Khorana AA, Noble S, Lee AYY, Soff G, Meyer G, O'Connell C, Carrier M. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH. *Blood.* 2019;133(14):291–298.
5. Rickles FR, Levine M, Edwards RL. Hemostatic alterations in cancer patients. *Thromb Res.* 2020;191:S1–S7.
6. Kwaan HC. Role of plasminogen activator inhibitor-1 in tumorigenesis. *Semin Thromb Hemost.* 2014;40(3):373–379.
7. Levi M, Iba T. COVID-19 coagulopathy: is it disseminated intravascular coagulation? *Blood Rev.* 2021;47:100702.
8. Placencio VR, DeClerck YA. Plasminogen activator inhibitor-1 in cancer: rationale and insight for future therapeutic testing. *Cancer Metastasis Rev.* 2020;39(4):923–935.
9. Heit JA, Spencer FA, White RH. The epidemiology of venous thromboembolism. *J Thromb Thrombolysis.* 2016;41(1):3–14.
10. Tripodi A. Hemostasis testing in the clinical laboratory. *Crit Rev Clin Lab Sci.* 2011;48(5-6):183–200.
11. Falanga A, Russo L, Milesi V, Vignoli A. Mechanisms and risk factors of thrombosis in cancer. *Crit Rev Oncol Hematol.* 2017;118:79–83.
12. Ay C, Pabinger I, Cohen AT. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost.* 2017;117(2):219–230.
13. Thaler J, Ay C, Pabinger I. Venous thromboembolism in cancer patients: risk factors and impact on survival. *Vasc Health Risk Manag.* 2012;8:153–163.
14. Lyman GH, Khorana AA. Cancer, clots and consensus: new understanding of an old problem. *J Clin Oncol.* 2009;27(29):4821–4826.
15. Connolly GC, Khorana AA. Emerging risk stratification approaches to cancer-associated thrombosis: risk factors, biomarkers and a risk score. *Thromb Res.* 2010;125 Suppl 2:S1–S7.
16. Timp JF, Braekkan SK, Versteeg HH, Cannegieter SC. Epidemiology of cancer-associated venous thrombosis. *Blood.* 2013;122(10):1712–1723.
17. Camerer E, Huang W, Coughlin SR. Tissue factor- and factor VIIa-dependent activation of PAR-2 by factor Xa. *Proc Natl Acad Sci USA.* 2000;97(10):5255–5260.
18. Zhang Y, Deng Y, Luther T, Müller M, Ziegler R, Waldherr R, Nawroth PP. Tissue factor controls the balance of angiogenic and antiangiogenic properties of tumor cells in mice. *J Clin Invest.* 1994;94(3):1320–1327.
19. Demers M, Wagner DD. NETosis: a new factor in tumor progression and cancer-associated thrombosis. *Semin Thromb Hemost.* 2014;40(3):277–283.
20. Varki A. Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood.* 2007;110(6):1723–1729.
21. Connors JM. Thrombophilia testing and venous thrombosis. *N Engl J Med.* 2017;377:1177–1187.
22. Lazo-Langner A, Goss GD, Spaans JN, Rodger MA. The effect of low-molecular-weight heparin on survival in cancer: a systematic review and meta-analysis. *J Thromb Haemost.* 2007;5(4):729–737.