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ORIGINAL RESEARCH

Clinical Significance of Factor XIII Activity and Monocyte-Derived Microparticles in Cancer Patients

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Background: The aim was to evaluate factor XIII activity (FXIIIa) and monocyte-derived microparticles (MDMPs) in cancer patients.

Methods: In total, 138 cancer patients (31 malignant lymphomas, 39 multiple myelomas, and 68 lung cancers) were analyzed. We measured various biomarkers including FXIIIa and MDMPs.

Results: The values of endothelial activation markers, monocyte chemoattractant peptide (MCP)-1, soluble (s)CD14, and MDMPs were higher in cancer patients than in non-cancerous controls. MCP-1, sCD14, and MDMPs were significantly correlated with FXIIIa in multivariate analysis in cancer patients. In addition, MCP-1, sCD14, and MDMP levels were significantly increased in the high FXIIIa group of patients. Finally, the survival rate of the high FXIIIa group was significantly poor in the Kaplan–Meier analysis.

Conclusion: These results suggest that abnormal levels of FXIIIa and MDMPs may offer promise as poor prognostic factors in cancer patients.

Keywords: factor XIII activity, cancer, thrombosis, endothelial cell, monocyte-derived microparticle, MDMP

Introduction

In recent years, oncocardiology has emerged as a new area of academic research, mainly in Europe and the United States.[1,2] Progression in cancer treatment including the development of molecular-targeted drugs has been made against this background.[3] While survival has improved, new cardiotoxicity or cardiovascular toxicity events due to such new treatments have been recorded. As a result, there is a growing need for cardiovascular treatment in parallel with cancer therapy.[4] The cardiotoxicity of chemotherapies is classified as heart failure, coronary heart disease, hypertension, thromboembolism, and arrhythmia.[5] Venous thromboembolism (VTE) is particularly important,[6] and came to be described as cancer-associated thrombosis (CAT) when VTE is related to cancer.[7] Cancer cells or the inflammatory region around cancer cells release substances that function in thrombosis such as tissue factor (TF), coagulation factor, or cytokines.[8] Vascular disorders, associated with chemotherapy or enhancement of the coagulation system, are important as factors of VTE.[9]

Factor XIII (FXIII) is present in the blood as a heterotetramer that is formed by FXIII-A and FXIII-B subunit polymers.[10] FXIII-A is present mainly in platelets, megakaryocytes, monocytes, and macrophages.[11,12] In contrast, FXIII-B is generated and secreted by liver cells, and binds to FXIII-A in peripheral blood.[10–12] FXIII is

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activated by thrombin which is produced in the final stages of coagulation, in a process called FXIII activity (FXIIIa).[11] FXIIIa forms covalent bonds between fibrins to eventually stabilize them.[11,12] Therefore, FXIII has an essential role in normal hemostasis, in which it contributes to the regulation of fibrinolysis.[13] Specifically, this factor contributes to clot strength in the final step of coagulation with platelets and fibrinogen. Additionally, functional cellular FXIII becomes exposed on the surface of stimulated platelets.[14] These observations suggest that a close relationship exists between activated platelets and FXIII. However, it has been reported that FXIII has various functions.[15–17] For example, high FXIIIa is associated with the risk of developing cardiovascular events.[18] Furthermore, abnormal FXIII expression levels or activity are found in some cancer patients.[19,20]

Activated monocytes and monocyte-derived microparticles (MDMPs) might be markers for vasculopathies in patients with lifestyle-related diseases.[21–23] In addition, monocyte chemotactic peptide (MCP)-1 is unregulated in some patients along with endothelial cell dysfunction markers such as soluble (s) E-selectin and soluble vascular cell adhesion molecule-1 (sVCAM-1).[24,25] However, little is known about FXIIIa and MDMPs in cancer patients. We investigated FXIIIa, MDMPs, and various biomarkers in cancer patients.

Materials and Methods

Subjects

Cancer patients and healthy volunteers were recruited from Kansai Medical Hospital and Kansai Medical University (Osaka, Japan) between August 2014 and September 2018. In total, 138 cancer patients were analyzed, and 14 had thrombotic complications within 6 months after their first examination. The types of cancer studied were malignant lymphoma (ML; n = 31), multiple myeloma (MM; n = 39), and lung cancer (LC; n = 68). The disease type of ML was classified using World Health Organization (WHO) classification 2017.[26] ML was classified into four stage (I, II, III and IV) by the Lugano classification.[27] The staging of MM was classified using the revised international staging system,[28] and LC stage was classified using the TNM classification of the international association for the study of LC.[29] This study was conducted in accordance with the Declaration of Helsinki and was performed with approval from the Institutional Review Board of Kansai Medical University. Written informed consent was obtained from all participants.

Measurement of FXIIIa

Patient blood samples (1.8 mL) were collected in 0.2 mL sodium citrate-containing tubes to a total volume of 2 mL. Citrated plasma was isolated by centrifugation for 15 min at 1500 ×g at 4°C. Plasma was divided into aliquots and FXIIIa was measured by photometric assay.[30] In a one-step procedure, FXIII was activated by thrombin, and Ca^{2+} and cross-linked glycine-ethyl ester to a specific glutamine-containing peptide substrate. The released ammonia was incorporated into alpha-ketoglutarate by glutamate dehydrogenase, and the NADH consumption of this reaction was measured photometrically at 340 nm. NADH-consumption was directly proportional to FXIIIa.

Measurement MDMPs

Blood samples were collected using a 21-gauge needle from a peripheral vein into vacutainers containing ethylenediaminetetraacetic acid (NIPRO Co. Ltd., Osaka, Japan) to minimize platelet activation. The samples were handled as described in the manufacturer's protocol. Briefly, the samples were gently mixed by inverting the tube once or twice, stored at room temperature for 2–3 h, and centrifuged at 8000 ×g for 5 min at room temperature. Storing samples at room temperature for 2–3 h did not affect MDMP levels. MDMPs were analyzed using an FACS Cant II flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA). All flow cytometry data of forward light scatter (FSC), side scatter (SSC), and fluorescence intensity (FL) were analyzed in log space. MDMPs were identified and quantified based on their FSC/SSC characteristics according to their size and reactivity to the monocyte-specific monoclonal antibody (CD14). The lower detection limit was placed at a threshold above the electronic background noise of the flow cytometer, and the upper threshold for FSC (1μm) was set with the use of standard beads (Megamix, BioCytex, Tokyo, Japan) (Figure 1A). To identify positively stained events, thresholds were set based on FITC-CD14 (G1 gate) (Figure 1B). Finally, events in the G1 gate were expanded to FSC/SSC (G2 gate) (Figure 1C). The density of MDMPs in the G2 gate was set to less than 10 events/μL using blood samples from healthy volunteers.

Measurement of MCP-1, sE-selectin, sVCAM-1, sCD14 and PAI-1

Patient blood samples were collected in empty or sodium citrate-containing tubes and left at room temperature for a minimum of 1 h. Serum and citrated plasma were

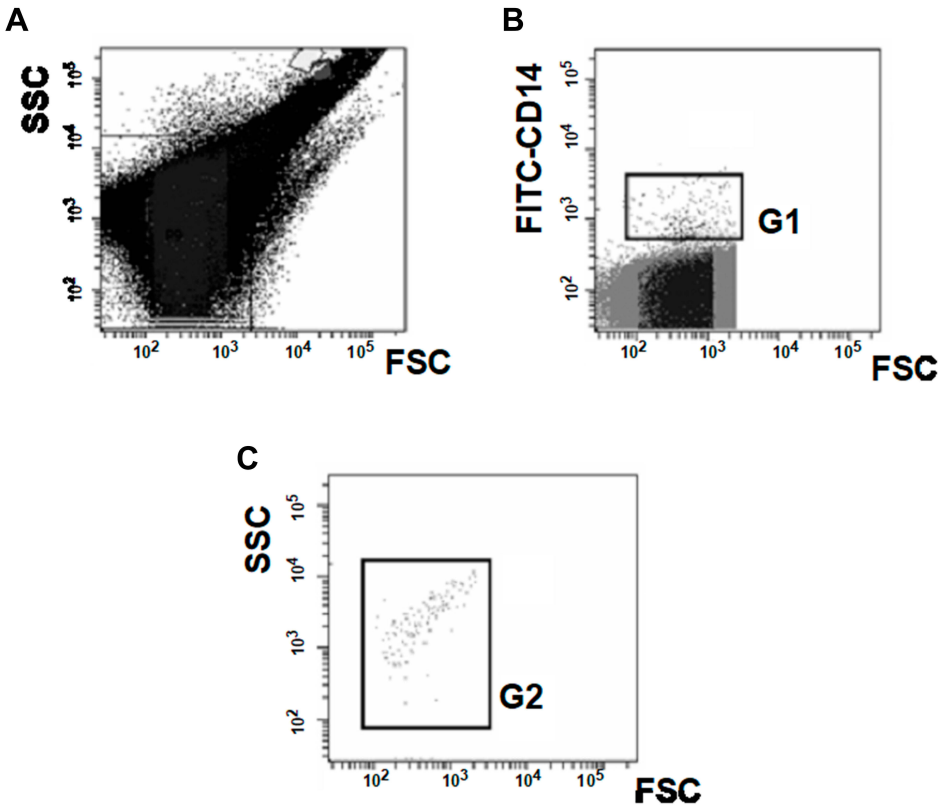

Figure 1 Gating and staining strategy for the detection of MDMPs in FACS analysis (**A**-**C**).
Abbreviations: SSC, side scatter; FSC, forward scatter.

isolated by centrifugation for 20 min at 1000 ×g at 4°C. Serum was divided into aliquots and frozen at −30°C until use. Recombinant products and standard solutions provided with commercial kits served as positive controls. Plasma concentrations of MCP-1, sE-selectin, sVCAM-1 and PAI-1 were measured using monoclonal antibody-based ELISA kits (Invitrogen, Carlsbad, CA, USA). Plasma sCD14 levels were measured by ELISA (R&D Systems Inc., Minneapolis, MN, USA). All kits were used according to the manufacturers' instructions.

Statistical Analysis

Data are expressed as mean ± standard deviation (SD) and were analyzed using multiple regression (stepwise method), as appropriate. A receiver operating characteristics (ROC) curve analysis was used to estimate the value of each biomarker. Between-group comparisons were made using the Newman–Keuls test and Scheffe's test. Overall survival (OS) was defined as the time from initial diagnosis to the time of death from any cause or the date the patient was last known to be alive. Univariate analyses of OS were performed using the Kaplan–Meier product-limit method with the Log-rank test and the Cox proportional hazards model. All statistical analyses were performed using StatFlex (v7) software, with $P < 0.05$ being considered statistically significant.

Results

Cell Type and Staging of Cancers of Cancer Patients

The types of ML examined in this study included 19 mature B cell lymphomas, 10 mature T/natural killer (NK) cell lymphomas, and two Hodgkin lymphomas. The frequency of stage III and IV in ML was 34%. All patients with MM were symptomatic myeloma,[31] and the frequency of stage III was 45%. The cell type of LC was 60 non-small cell and eight small cell LC. The frequency of stage IIIb and IV was 56%. The mortality rate during the observation period was 32% (ML, 5/31; MM, 10/39; and LC, 32/68).

Clinical Characteristics of Cancer Patients

Patient demographic and clinical characteristics are shown in Table 1. We confirmed that all biomarker values were

Table 1 Demographic and Clinical Characteristics of Cancer Patients and Healthy Controls

	Control	Cancer Patients	p value
n	40	138	
Men/women (no.)	26/14	81/57	
Age (years)	42 ± 11	53 ± 13	0.1946
BMI (kg/m^2)	25.1 ± 6.2	25.3 ± 9.2	0.6149
WBC (/μl)	58 ± 13	61 ± 24	0.5362
Hb (g/dL)	14.5 ± 2.9	12.7 ± 8.8	0.0175*
ROW-SD (fl)	43.3 ± 10.5	61.4 ± 22.6	0.0074*
Plt (×10^4/μl)	24.5 ± 3.9	27.3 ± 7.8	0.1375
MPV (fl)	9.12 ± 0.51	10.13 ± 1.13	0.0086*
FXIIIa (%)	89.2 ± 10.3	98.5 ± 13.2	0.0225*
sE-selectin (ng/mL)	43 ± 12	59 ± 26	0.0122*
sVCAM-1 (ng/ml)	613 ± 181	1556 ± 822	0.0094*
PAI-1 (ng/mL)	9.1 ± 2.7	36.2 ± 8.1	0.0012*
MCP-1 (pg/ml)	395 ± 91	482 ± 126	0.0338*
sCD14 (μg/mL)	2.3 ± 0.8	3.9 ± 1.2	0.0362*
MDMP (ev/μl)	39.4 ± 8.2	56.3 ± 10.2	0.0133*

Notes: Data are shown as mean ± SD. *Indicates statistical significance (P<0.05).
Abbreviations: BMI, body mass index; WBC, white blood cells; Hb, hemoglobin; RDW-SD, red blood cell distribution width-standard deviation; Plt, platelet count; MPV, mean platelet volume; FXIIIa, factor XIII activity; sE-selectin, soluble E-selectin; sVCAM-1, soluble VCAM-1; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemotactic peptide; sCD14, soluble CD14; MDMPs, monocyte-derived microparticles.

Table 2 Multiregression Analysis of FXIIIa in Cancer Patients

	Univariate	p value	Multivariate	
	β		β	p value
Age (years)	0.2362	0.08162		
Sex (men)	− 0.0673	0.37952		
BMI (kg/m^2)	0.2361	0.96373		
WBC (/μl)	0.1759	0.28345		
Hb (g/dL)	0.2392	0.09857		
RDW-SD (fl)	0.3276	0.04811*	0.2336	0.11324
Plt (×0^4/μl)	0.3961	0.00923*	0.2751	0.07312
MPV (fl)	0.4355	0.00162*	0.3154	0.05982
sE-selectin (ng/mL)	0.3823	0.00713*	0.2861	0.06239
sVCAM-1 (ng mL)	0.4379	0.00192*	0.3365	0.04125*
PAI-1 (pg/mL)	0.4682	0.00188*	0.3589	0.01142*
MCP-1 (pg/mL)	0.5122	0.00136*	0.4327	0.03512*
sCD14 (μg/mL)	0.4962	0.00274*	0.3986	0.05013
MDMP (ev/μl)	0.6235	0.00018*	0.5943	0.00951*

Notes: β indicates standardized regression coefficients. *Indicates statistical significance (P<0.05).
Abbreviations: BMI, body mass index; WBC, white blood cells; Hb, hemoglobin; RDW-SD, red blood cell distribution width-standard deviation; Plt, platelet count; MPV, mean platelet volume; FXIIIa, factor XIII activity; sE-selectin, soluble E-selectin; sVCAM-1, soluble VCAM-1; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemotactic peptide; sCD14, soluble CD14; MDMPs, monocyte-derived microparticles.

distributed normally, and we estimated the value of each biomarker using a ROC curve. Age, body mass index (BMI), white blood cells and platelets were similar in the cancer and the non-cancer controls. Hb in cancer patients was significantly lower than the non-cancerous controls. However, the values of red blood cell distribution width (RDW)-SD, mean platelet volume (MPV), FXIIIa, sE-selectin, sVCAM-1, PAI-1, MCP-1, sCD14, and MDMPs were higher in cancer patients than the healthy controls.

Univariate and Multivariate Regression Analyses

We investigated the associations between 14 variables and FXIIIa in cancer patients (Table 2). Univariate analysis showed that RDW, platelets, MPV, sE-selectin, sVCAM-1, PAI-1, MCP-1, sCD14, and MDMPs were factors significantly associated with FXIIIa, whereas sVCAM-1, PAI-1, MCP-1, sCD14, and MDMPs were significantly correlated with FXIIIa in multivariate analysis.

Comparison of All Markers of High FXIIIa or Non-High FXIIIa Groups in Cancer Patients

We calculated the cutoff value for FXIIIa using ROC curve analysis. A cutoff value of 108.23 was found to be an identifying value for patients with cancers. We divided the patients with cancer into two groups according to the cutoff value of 108.23 for FXIIIa. There were no significant differences in age, BMI, WBC, Hb, RDW-SD, platelets and MPV between the non-high FXIIIa and high FXIIIa groups (Table 3). However, sE-selectin, sVCAM-1, PAI-1, MCP-1, sCD14 and MDMP levels were significantly increased in the high FXIIIa group (Table 3).

Kaplan–Meier Curves of Non-High FXIIIa and High FXIIIa Patient Groups

Figure 2 shows the Kaplan–Meier curves for OS of the cancer patients with or without high FXIIIa. The log-rank P-value at 2000 days between patients with or without high FXIIIa was 0.032.

Discussion

It has been known for some time that cancer is accompanied by the risk of thrombosis such as Trousseau's syndrome.[32,33] It is necessary to consider the thrombosis associated with the treatment for cancer separately from the original risk of cancer itself.[9] In addition, even if the cancer treatment is successful, we have to consider the other factors or side effects of anticancer drugs. Therefore, predicting CAT is an important proposition for cancer in clinical practice. Several biomarkers have been reported in

Table 3 Plasma Levels of Various Biomarkers in the Non-High FXIIIa and High FXIIIa Groups

	Non-High FXIIIa Group	High FXIIIa Group	p value
n	80	58	
Men/women (no.)	50/30	31/27	
Age (years)	51 ± 14	54 ± 12	0.6347
BMI (kg/m^2)	25.1 ± 7.4	25.5 ± 9.6	0.5988
WBC (/μl)	59 ± 19	63 ± 25	0.5873
Hb (g/dL)	13.1 ± 8.3	11.9 ± 9.5	0.2139
RDW-SD (fl)	56.4 ± 17.5	63.9 ± 24.2	0.0512
Plt (x10^4/μl)	23.9 ± 8.2	28.1 ± 10.2	0.0577
MPV (fl)	8.69 ± 0.93	10.92 ± 1.59	0.0538
sE-selectin (ng/mL)	51 ± 22	66 ± 29	0.0414*
sVCAM-1 (ng/ml)	1421 ± 733	1678 ± 925	0.0322*
PAI-1 (ng/mL)	25.1 ± 6.3	41.4 ± 8.1	0.0013*
MCP-1 (pg mL)	439 ± 112	482 ± 10.2	0.0105*
sCD14 (μg/mL)	3.7 ± 0.9	4.3 ± 1.6	0.0436*
MDMP (ev/μl)	50.2 ± 7.8	63.9 ± 15.1	0.0047*

Notes: Data are shown as mean ± SD. *P*-value, non-high FXIIIa group versus high FXIIIa group. *Indicates statistical significance ($P<0.05$).

Abbreviations: BMI, body mass index; WBC, white blood cell; Hb, hemoglobin; RDW-SD, red blood cell distribution width-standard deviation; Plt, platelet count; MPV, mean platelet volume; FXIIIa, factor XIII activity; sE-selectin, soluble E-selectin; sVCAM-1, soluble VCAM-1; PAI-1, plasminogen activator inhibitor-1; MCP-1, monocyte chemotactic peptide; sCD14, soluble CD14; MDMPs, monocyte-derived microparticles.

terms of CAT predictions thus far.[34–39] Zöller et al[34] reported that RDW-SD is associated with long-term incidence of the first event of VTE among middle-aged subjects, although not necessarily cancer. Other reports suggest that MPV is associated with VTE risk and survival in cancer patients.[35–37] In the present study, we observed the high level of RDW-SD, MPV, sE-selectin, sVCAM-1, PAI-1, MCP-1 and sCD14 in cancer patients, although we could not recognize the significance of these markers in

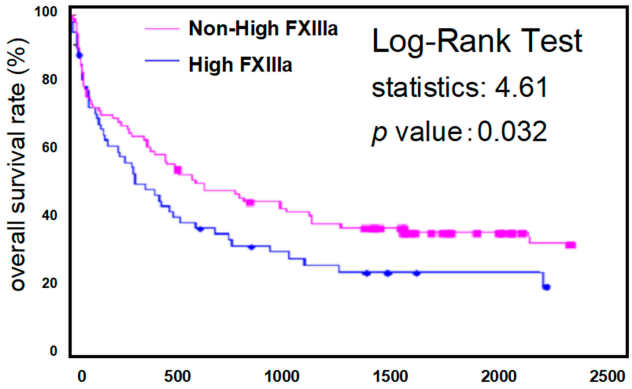

Figure 2 Kaplan–Meier curves of overall survival of non-high FXIIIa and high FXIIIa patient groups.

Abbreviation: FXIIIa, factor XIII activity.

CAT. However, an interesting marker was MDMP, because MPs could associate with CAT.[38–43]

MDMPs contribute to the development of thrombosis at sites of vascular injury, since they express TF and enhance the exogenous tract of coagulation.[44] The binding of these MDMPs to activated endothelial cells may promote the accumulation of tissue factor and localize thrombin generation, resulting in the development of thrombosis.[34,45] Some previous reports demonstrated the importance of tumor-derived MPs in CAT or the increased levels of TF-positive MPs in cancer patients with VTE compared with cancer patients without VTE.[39–43] Furthermore, prospective studies suggested that high levels of TF-positive MPs activity may predict VTE in cancer patients.[37–39] A meta-analysis by Cui et al[38] demonstrated the increased presence of TF-positive MPs that represented an increased risk of CAT with overall odds of 1.76. In addition, the role of TF-positive MPs originating from tumor cells in CAT development has been clearly shown in human pancreatic BxPc-3 cells orthotopically grown in nude mice.[46,47] Thus, TF-positive MPs including MDMPs have an important role in CAT. Interestingly, in the present study, MDMP significantly increased in cancer patients compared with healthy controls. However, CAT appears to be involved in the mechanism of TF-independent MDMP.[48] This suggests that it is necessary to consider another role of MDMP other than coagulofibrinolytic imbalance in CAT as a future potential therapeutic target.

Abnormal FXIIIa appears to cause thrombotic states such as cardiovascular diseases.[18,49,50] The same abnormal activity has been reported in cancer patients.[17,20] A study in non-small cell lung cancer found that FXIIIa levels in advanced-stage patients are higher than those in healthy controls. These patients indicated that FXIIIa expression could potentially be used as a predictive marker of advanced non-small cell lung cancer.[20] In the present study, FXIIIa was significantly increased in cancer patients compared with healthy controls. In the present study, the frequency of patient with advanced cancer was 34% in ML, 45% in MM and 56% in LC. Unfortunately, we could not confirm a significant elevation of FXIIIa in these advanced cases. Therefore, the expression of FXIIIa by tumor-infiltrating macrophages was not determined. In the present study, MCP-1, sCD14 and MDMPs were higher in cancer patients than in non-cancerous controls. In addition, the levels of these markers were significantly increased in the high-FXIIIa group. These findings suggest that the association of monocytes and FXIIIa occurs in cancer

patients, resulting in the poor prognosis of the high-FXIIIa cancer patients in our Kaplan–Meier analysis. However, the role of FXIII in CAT is still unclear, and the relationship between FXIII and cancer needs to be further elucidated.

Conclusions

In conclusion, RDW-SD, MPV, FXIIIa, sE-selectin, sVCAM-1, PAI-1, MCP-1, sCD14, and MDMP levels were higher in cancer patients than in non-cancerous controls. sVCAM-1, PAI-1, MCP-1, sCD14, and MDMPs were significantly correlated with FXIIIa by multivariate analysis in cancer patients. In addition, sE-selectin, sVCAM-1, PAI-1, MCP-1, sCD14, and MDMP levels were increased significantly in the high FXIIIa group. Finally, the survival rate of the high-FXIIIa group was significantly poor in the Kaplan–Meier analysis. Therefore, abnormal levels of FXIIIa and MDMPs may offer promise as poor prognostic factors in cancer patients.

Nevertheless, this study has some limitations. First, we could not confirm a direct relationship of FXIIIa or MDMPs in our thrombotic patients. Second, we did not attempt a more accurate method than flow cytometry to detect MDMPs. For example, antigenic detection of TF-positive MDMPs by scanning confocal microscopy may be appropriate.[48,51,52] These limitations are issues to be considered in the future.

Abbreviations

RDW-SD, red blood cell distribution width-standard deviation; MPV, mean platelet volume; FXIIIa, factor XIII activity; MCP-1, monocyte chemotactic peptide-1; sCD14, soluble CD14; BMI, body mass index; TF, tissue factor; sE-selectin, soluble E-selectin; sVCAM-1, soluble vascular cell adhison molecule-1; PAI-1, plasminogen activator inhibitor-1; MDMP, monocyte-derived microparticle; LC, lung cancer; ML, malignant lymphoma; MM, multiple myeloma; CAT, cancer-associated thrombosis; VTE, venous thromboembolism.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that there are no conflicts of interest.

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