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LETTER TO THE EDITOR

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A new risk-assessment tool for venous thromboembolism in advanced lung cancer: a prospective, observational study

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Abstract

Management of cancer-associated venous thromboembolism (VTE) is essential in treatment selection and cancer prognosis. However, to date, there is no method to assess the risk of VTE specifically associated with advanced lung cancer. Our aim was to create a new risk assessment scoring system that can predict the concomitant or incidence of VTE in advanced lung cancer. We used the dataset of 1008 patients with lung cancer in the Rising-VTE/NEJ037 study, of which 100 (9.9%) developed VTE. The items extracted in the multivariate analysis included female sex, adenocarcinoma, performance status, N factor, lymphocyte count, platelet count, prothrombin fragment 1 + 2, and diastolic blood pressure. This model had a maximum score of 8 points, with ≥ 5 points indicating a high risk of VTE. This simple risk-assessment model for VTE complications with advanced lung cancer could help identify cases that required monitoring for VTE.

Keywords: Deep vein thrombosis, Pulmonary thromboembolism, Lung cancer, Risk-assessment model, Prothrombin fragment 1 + 2

To the editor

Venous thromboembolism (VTE) is a common medical complication of cancer treatment, and the risk of developing VTE is particularly high in lung cancer patients [1]. Numerous risk score tools to evaluate cancer-associated VTE have been proposed [2, 3]. The Khorana score [2] is the most widely used risk assessment tool for patients scheduled to receive chemotherapy. A meta-analysis reported that the performance of the Khorana score for lung cancer differed from that for other types of cancer and that it was not useful in predicting VTE in lung cancer [4]. As the efficacy of advanced and personalized lung cancer treatments can be maximized by optimally managing complications, such as VTE, there is an urgent need to establish a VTE risk assessment scoring system for lung cancer patients scheduled to receive chemotherapy.

The Rising-VTE/NEJ037 Study, a physician-led, multicenter, prospective, observational study, attempted to identify the incidence of VTE and its risk factors while treating lung cancers for which radical treatments were unsuitable (manuscript in preparation). To our knowledge, the Rising-VTE/NEJ037 Study is the largest prospective study involving intensive screening programs for VTE at the time of cancer diagnosis, along with a further follow-up to assess the incidence of VTE. As many

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cases of VTE co-developing with lung cancer are asymptomatic, an appropriate risk-assessment scoring system is essential to identify the types of patients who should undergo aggressive screening and monitoring. Here, we describe a newly created risk-assessment scoring system that can predict the co-development or incidence of VTE in advanced lung cancers using the Rising-VTE/NEJ037 Study dataset.

The Rising-VTE/NEJ037 Study included 1008 patients comprising the whole analysis set diagnosed with lung cancer unsuitable for radical resection or radiation between June 2016 and August 2018 across 35 institutions in Japan. The parameters used for risk assessment included age, sex, body mass index, histological classification of the cancer, TNM factors, performance status scores, past medical history, comorbidities, complete blood cell count, coagulation markers (D-dimer, prothrombin fragment 1 + 2 [PT F1 + 2]), liver function markers, kidney function markers, electrolyte levels, C-reactive protein levels, brain natriuretic peptide levels, oxygen saturation, blood pressure, epidermal growth factor receptor gene mutation status, and anaplastic lymphoma kinase fusion gene. We performed a multivariate analysis by logistic regression analysis using a stepwise method to extract the relevant risk factors for VTE. Candidate factors were extracted, and a tenfold cross-validation was used to create a risk-assessment scoring system that ensured internal validity. Receiver operating characteristic (ROC) analysis was performed to estimate the respective cut-off values for each item in the scoring process. The eight risk factors identified by multivariate analysis were evaluated in the ROC analysis, and cut-off values were set (Table 1). The ROC AUC (0.751) indicated a sufficient discriminating ability (Fig. 1).

To our knowledge, this is the first study to show that low PLT counts and elevated DBP are risk factors for VTE. Additionally, we revealed that an elevated D-dimer level is not a risk factor and that PT F1 + 2 is a more suitable serum marker involved in coagulation for risk identification. PT F1 + 2 has been reported to be particularly useful as a predictor of cancer-associated thrombosis

Table 1 New risk scoring system created from the extracted VTE risk factors

Parameter	Coefficient	OR	95% CI	*p*-value	Score point
Overview of the risk score					
Sex, Female (vs. Male)	0.730	2.076	1.257–3.429	0.004	1
Adenocarcinoma (vs. non-small cell lung cancer, others)	0.845	2.327	1.277–4.241	0.006	1
N type, 3 (vs. 0–2)	0.754	2.125	1.299–3.475	0.003	1
Eastern Co-operative Oncology group performance status, 1–3 (vs. 0)	0.754	2.125	1.220–3.704	0.008	1
Lymphocyte percentage < 18%	0.763	2.145	1.293–3.557	0.003	1
Platelet count < 280,000/μL	0.747	2.110	1.238–3.595	0.006	1
Prothrombin fragment 1 + 2 ≥ 325 pmol/L	0.768	2.155	1.313–3.535	0.002	1
Diastolic blood pressure ≥ 70 mmHg	0.658	1.931	1.122–3.325	0.018	1

Points calculated from score	VTE incidence rate
Estimation of the VTE incidence rate using the new risk-assessment scoring system	
0	0.003
1	0.007
2	0.015
3	0.031
4	0.064
5	0.127
6	0.237
7	0.398
8	0.584

Cut-off values for lymphocyte percentage, platelet count, prothrombin fragment 1 + 2 level, and diastolic blood pressure were estimated by ROC analysis

As VTE was observed in 100 of the 1008 cases (incidence rate: 0.099) in the Rising-VTE/NEJ037 Study, scores ≥ 5 were classified into the high-risk group

VTE, venous thromboembolism; CI, confidence interval; OR, odds ratio

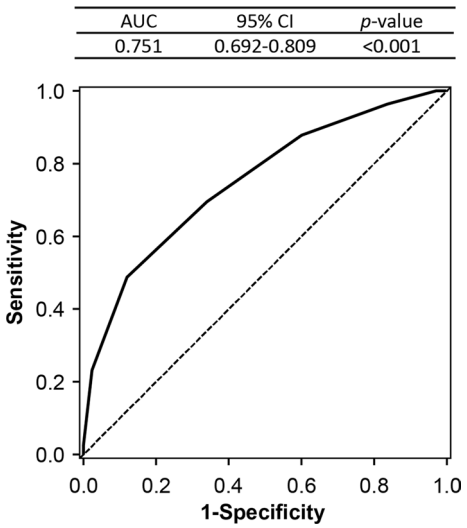

Fig. 1 Evaluation of the discriminating ability of the new VTE risk scoring system (receiver operating characteristic curve)

when used in combination with D-dimer [5]; its usefulness should be verified in future studies.

As cancer-related VTEs are often asymptomatic, risk scores that help actively screen patients at high risk of developing VTE are clinically important. Furthermore, identifying patient populations at a high risk of developing VTE using a thoroughly tested risk-assessment scoring system can balance the complications from adverse events, such as bleeding, with the benefits of prophylactic treatments administered for VTE in patients scheduled to receive chemotherapy. Therefore, our proposed predictive scoring system for the risk of VTE onset in advanced lung cancers may have great value in clinical settings.

This study had some limitations. Whether our proposed risk scoring system would be useful in non-Japanese patients should be examined. In addition, although it underwent internal validation, external validation by other studies is required. We expect that with an increase in the number of cancer patients achieving long-term survival, there will be a greater focus on the diagnosis and treatment of VTE co-developing with cancer in the future.

Abbreviations

AUC: Area under the curve; CRP: C-reactive protein; CT: Computed tomography; DBP: Diastolic blood pressure; DOAC: Direct oral anticoagulant; DVT: Deep-vein thrombosis; EDO: Edoxaban; NCCN: National Comprehensive Cancer Network; PLT: Platelet; PT F1 + 2: Prothrombin fragment 1 + 2; ROC: Receiver operating characteristic; VTE: Venous thromboembolism.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-022-01259-7.

Additional file 1. Supplemental methods

Additional file 2. Patient characteristics at the time of lung cancer diagnosis

Additional file 3. Univariate analysis of VTE risk

Additional file 4. Proposed new risk score

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Author contributions

YT was involved in conceptualization of the study, methodology, investigation, data curation, and writing of the manuscript; TH was involved in data curation, methodology, investigation, and writing of the manuscript; KH, NF, TY, RS, AN, TM, MH, SK, RH, TS, and MN were involved in the investigations and writing of the manuscript; MY, NI, KF, TK, and KK were involved in the methodology, investigations, and writing of the manuscript; and TI was involved in conceptualization of the study and writing of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice Guidelines. The study protocol was approved by the Shimane University Institutional Review Board based on the Clinical Trials Act enacted in Japan in 2017 and published in the Japan Registry of Clinical Trials (jRCTs061180025). Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

Outside of the submitted work, YT received personal fees and a grant from Daiichi Sankyo Co., Ltd. and AstraZeneca K.K. and personal fees from Chugai Pharmaceuticals Inc.; NF received personal fees from AstraZeneca K.K., Chugai Pharmaceutical, Nippon Boehringer Ingelheim Co., Ltd., Bristol-Myers Squibb Company, Eli Lilly Japan K.K., MSD K.K., Pfizer Japan Inc. Taiho Pharmaceutical, and Novartis Pharma K.K.; TY received personal fees from Eli Lilly Japan K.K., Merck Sharp & Dohme K.K., and Takeda Pharmaceutical; AN received personal fees and a grant from AstraZeneca K.K., Thermo Fisher Scientific, Inc., Chugai Pharmaceutical Co., Ltd., Eli Lilly Japan K.K., Novartis Pharma K.K., Pfizer Japan Inc., and Nippon Kayaku Co., Ltd. and personal fees from Taiho Pharmaceutical Co., Ltd.; TM received personal fees from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Eli Lilly Japan, Nippon Boehringer Ingelheim Co., Ltd., Kyowa Kirin Co., Ltd., and Ono Pharmaceutical Co., Ltd.; KF received personal fees from AstraZeneca K.K., Chugai Pharmaceutical Co., Ltd., Bristol-Myers Squibb Company, MSD K.K., Pfizer Japan Inc., Daiichi Sankyo Co., Ltd., Eli Lilly Japan, and Nippon Boehringer Ingelheim Co., Ltd.; KK received

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