学 位 論 文 の 要 旨

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学 位 論 文 名　D-dimer Cut-off Value for Predicting Venous Thromboembolism at the Initial Diagnosis in Japanese Patients with Advanced Lung Cancer

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論 文 内 容 の 要 旨

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major complication in patients with malignant diseases. Lung cancer is known to be one of the malignancies most strongly associated with VTE. The development of VTE adversely affects prognosis, quality of life, and treatment continuity. Furthermore, a substantial proportion of VTE cases in patients with advanced lung cancer are asymptomatic and are detected incidentally during routine imaging examinations. Early identification of these patients is important because untreated VTE may result in life-threatening complications.

D-dimer, a fibrin degradation product, is widely used as a screening biomarker for VTE. However, the diagnostic performance of D-dimer is reduced in cancer patients because malignancy itself is associated with activation of the coagulation system and elevated baseline D-dimer levels. Consequently, the conventional cut-off value used in the general population often results in low specificity and unnecessary imaging studies in patients with cancer. Although several studies have evaluated the relationship between D-dimer levels and VTE in cancer patients, an optimal D-dimer threshold for predicting VTE at the time of initial diagnosis has not been established in Japanese patients with advanced lung cancer. Therefore, the aim of

this study was to determine the optimal D-dimer cut-off value for predicting concomitant VTE at the initial diagnosis of advanced lung cancer in Japanese patients.

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of Shimane University.

This study was conducted as a post-hoc analysis of the Rising-VTE/NEJ037 study, a prospective multicenter observational study designed to evaluate the incidence and clinical impact of VTE in Japanese patients with advanced lung cancer (jRCT registration number: 061180025).

Eligible patients were newly diagnosed with advanced lung cancer and were not candidates for curative surgery or definitive radiotherapy. Patients whose plasma D-dimer levels were measured at the time of diagnosis were included in the present analysis. Screening for VTE was performed using contrast-enhanced computed tomography covering the chest, abdomen, pelvis, and lower extremities, or lower-extremity venous ultrasonography. VTE was diagnosed based on imaging findings.

Baseline clinical characteristics including age, sex, body mass index, Eastern Cooperative Oncology Group performance status, histological subtype, and disease stage were collected. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal D-dimer cut-off value. The area under the ROC curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

RESULTS AND DISCUSSION

A total of 976 patients with advanced lung cancer were included in the analysis. VTE was identified in 62 patients (6.3%) at the time of diagnosis. Importantly, 51 of these patients (82.3%) were asymptomatic, highlighting the importance of appropriate screening strategies.

The median D-dimer level was significantly higher in patients with VTE than in those without VTE (7.7 μg/mL versus 1.4 μg/mL, $P < 0.001$). ROC curve analysis demonstrated an AUC of 0.794 (95% confidence interval, 0.725–0.863), indicating good discriminatory ability. The optimal D-dimer cut-off value for predicting VTE was determined to be 3.3 μg/mL. At this threshold, the sensitivity was 74.2% and the specificity was 78.2%. The NPV was 97.8%, whereas the PPV was 18.7%.

The identified cut-off value was substantially higher than the conventional threshold commonly used in the general population. This finding likely reflects the hypercoagulable state associated with advanced malignancy, in which cancer-related inflammation and coagulation activation elevate baseline D-dimer levels even in the absence of VTE. The high NPV observed at the 3.3 μg/mL threshold suggests that this value may be useful for excluding VTE at the time of diagnosis in patients with advanced lung cancer.

This study has several strengths. It was based on a large prospective multicenter cohort and evaluated patients at the clinically important time point of initial diagnosis. However, several limitations should be considered. First, this was a post-hoc analysis and residual confounding cannot be excluded. Second, the findings may not be directly applicable to non-Japanese populations or patients with early-stage lung cancer. Nevertheless, the present study provides clinically relevant evidence regarding D-dimer-based screening for VTE in Japanese patients with advanced lung cancer.

CONCLUSION

A D-dimer cut-off value of 3.3 μg/mL demonstrated the best balance between sensitivity and specificity for predicting VTE at the initial diagnosis of advanced lung cancer in Japanese patients. This threshold may be useful for identifying patients who warrant further evaluation for VTE and may contribute to more efficient screening strategies in clinical practice.