

Peer Review File

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Reviewer A

Comment 1: What is the fate, the destiny of patients with lung cancer and DVT or PE? what is the impact of PE and DVT on survival and prognosis? I think that is a crucial argument;

Reply 1: Thanks for your constructive suggestions. According to the previous study, VTE patients have a three-fold higher risk of 1-year mortality compared to those without thrombotic complications. The hazard ratio for mortality at one year for patients with a VTE was 2.01 ($p < 0.001$). Patients suffering VTE had reduced 5-year survival. Accordingly, strategies to reduce VTE risk should be considered in patients undergoing high risk operations to reduce the mortality of VTEs. As described in our paper, PE is a common fatal emergency, manifested as a blockage in one of the pulmonary arteries. PE has gradually become the third major cause of death from cardiovascular and cerebrovascular diseases .

Reference

Corrales-Rodriguez L, Blais N. Lung cancer associated venous thromboembolic disease: a comprehensive review. *Lung Cancer*. 2012;75(1):1-8. doi:10.1016/j.lungcan.2011.07.004

Akhtar-Danesh GG, Akhtar-Danesh N, Shargall Y. Venous Thromboembolism in Surgical Lung Cancer Patients: A Provincial Population-Based Study. *Ann Thorac Surg*. 2022;114(3):890-897. doi:10.1016/j.athoracsur.2021.10.018

Lehnert P, Lange T, Møller CH, Olsen PS, Carlsen J. Acute Pulmonary Embolism in a National Danish Cohort: Increasing Incidence and Decreasing Mortality. *Thromb Haemost*. 2018;118(3):539-546. doi:10.1160/TH17-08-0531

Comment 2: Statistical analysis paragraph: the t-test is currently used for normally distributed data resumed with mean and standard deviation. The authors should declare how the data are distributed and also how the data are resumed;

Reply 2: SPSS version 22.0 (IBM, Armonk, NY, USA) was used for statistical analysis. Normal distribution quantitative data (i.e. patients' age, coagulation determinations) were expressed as mean \pm SD and Student's t-test was used for continuous variables and the chi-square or Fisher's exact tests were used for comparison of categorical variables.

Changes in the text: We have added in Page 6, line 13-15.

Comment 3: Paragraph methods: I suggest inserting a sentence describing the comparison between the two groups of patients: DVT with PE and DVT without PE.

Reply 3: Thank you very much for pointing out this issue. We have added it in the text: Among DVT types, the PE group had more mixed DVT cases than those in the non-PE group, but the difference was not significant after multivariate analysis.

Changes in the text: Page 7, line 14-16.

Comment 4: Paragraph results: the sentences in p5127-30 are not completely clear: what was the mean of suspicious clinical features? these features should be completely defined before showing the results.

Reply 4: Thanks for your constructive suggestions, which are helpful for improving our manuscript. We added the mean of suspicious clinical features in the text.

Changes in the text: Page 7, line 32; Page 8, line 1.

Comment 5: Regarding the score, I suggest inserting a table that resumes the score variables with the points for each variable

Reply 5: Thanks for pointing out this issue. This paper analyzed PE in lung cancer patients with lower limb deep venous thrombosis by the degree of risk factors and did not study the specific score value. We will further expand the data for analysis in future studies.

Comment 6: Table 1: what surgery means? Surgery is performed before the identification of DVT and PE? When surgery is performed? Surgery is a well known risk factors of DVT and PE and every patients must be treated with prophylactic low molecular weight heparin to reduce the risk of DVT and PE as the recent guidelines suggest.

Reply 6: According to the 2022 International Clinical Practice Guidelines: Low-molecular-weight heparin (LMWH) is recommended in VTE prophylaxis in cancer patients undergoing surgery. In this study, the samples were patients with lung adenocarcinoma confirmed stage IA. No anticoagulation therapy is received without special circumstances. The surgery mentioned in this study refers to the surgery at different parts (gynecological, gastrointestinal, hip or knee replacement, other orthopedic surgery, etc.) and not lung cancer surgery only. According to previous studies, the risk of VTE peaked within the first month after surgery. Our study surgery means the surgical trauma performed within one month before the definite diagnose. Furthermore The exclusion criteria in our study has included any anticoagulant treatment prior to admission.

Reference:

Farge D, Frere C, Connors JM, et al. 2022 international clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer, including patients with COVID-19. *Lancet Oncol.* 2022;23(7):e334-e347. doi:10.1016/S1470-2045(22)00160-7

Akhtar-Danesh GG, Akhtar-Danesh N, Shargall Y. Venous Thromboembolism in Surgical Lung Cancer Patients: A Provincial Population-Based Study. *Ann Thorac Surg.* 2022;114(3):890-897. doi:10.1016/j.athoracsur.2021.10.018

Changes in the text: Page 6, line 8-9.

Comment 7: table 1: I suggest inserting the clinical stage because high clinical stage is well known risk factor of DVT and PE;

Reply 7: Thanks for your kind advice. The cases included in the study were all patients with stage I lung adenocarcinoma without metastasis. We have mentioned it the text.

Changes in the text: Page 5, line 6.

Comment 8: table 3: I suggest modifying the table merging the table of univariate analysis and multivariable analysis of the all clinical variables included into the logistic regression model.

These are some suggestions that, in my opinion, could improve the paper quality and strength.

Reply 8: Thanks for your constructive suggestions. Table 1 showed all the research factors. The factors considered statistically significant by univariate analysis were further analyzed by multiple factors to obtain risk factors, which were clearly shown in Table 3. Table 1 to Table 3 is a process that we studied, and we referred to other literature as list:

Shi H, Guo LH, Zhang YF, et al. Suspicious ultrasound and clinicopathological features of papillary thyroid carcinoma predict the status of TERT promoter. *Endocrine*. 2020;68(2):349-357. doi:10.1007/s12020-020-02214-7

Chen J, Li XL, Zhao CK, et al. Conventional Ultrasound, Immunohistochemical Factors and BRAFV600E Mutation in Predicting Central Cervical Lymph Node Metastasis of Papillary Thyroid Carcinoma. *Ultrasound Med Biol*. 2018;44(11):2296-2306. doi:10.1016/j.ultrasmedbio.2018.06.020

Changes in the text: Page 6, line 17-18.

Reviewer B

Comment 1: The authors show being bedridden for long periods and elevated serum D-dimer levels as predictors of PE in lung cancer patients, but these factors likely to be caused by disease progression such as decreased performance status and trousseau syndrome. Have the authors analyzed statistical relationship between clinical stages of lung cancer and PE?

Reply 1: Thanks for your kind advice. The cases included in the study were all patients with stage I lung adenocarcinoma without metastasis. We have mentioned it the text. The relationship between clinical stages of lung cancer and PE is a valuable research aspects and it will be further deepened in our next research work.

Changes in the text: Page 5, line 6.

Comment 2: Hypercoagulable state associated with lung cancer such as trousseau syndrome more likely to be observed in advanced lung adenocarcinoma. Please provide histopathological types of lung cancer as clinical characteristics of patients with lung cancer and DVT in Table

Reply 2: Thanks for your kind advice. The cases included in the study were all patients with stage I lung adenocarcinoma without metastasis. We have mentioned it the text.

Changes in the text: Page 5, line 6.

Comment 3: On page 5, the authors mentioned all variables with $P < 0.05$ in univariate regression analyses were tested by multivariate analysis. The results of univariate analysis should be shown.

Reply 3: Thanks for your constructive suggestions, which is helpful for improving our manuscript. We have mentioned the results of univariate analysis in the text.

Changes in the text: Page 7 line 11-14

Comment 4: Were there any patients who had not received ultra sound during the study period? If some patients had not received US, there would be a large bias. In the limitation section, the authors need to describe this bias.

Reply 4: Thanks for your kind advice. The cases in the study all received ultrasound during the study period. We have mentioned it the inclusion criteria. (Page5, line7.)

Comment 5: In figure 2, match the symbols in figures and figure legends (a-f or A-F).

Reply 5: Thank you very much for the constructive suggestion and kind recommendation. We have matched the symbols in figures and figure legends (A-F).

Changes in the text: Page 18, line 3-8.

Comment 6: Please provide the approval number of IRB.

Reply 6: The study was approved by the ethical committee of the Shanghai Chest Hospital (No. KS1956) .We have mentioned in the text.

Changes in the text: Page 5, line 14-17.