Original Article

Incidence of venous thromboembolism and hemorrhage in Chinese patients after pulmonary lobectomy: mechanical prophylaxis or mechanical prophylaxis combined with pharmacological prophylaxis: a randomized controlled trial

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Background: Venous thromboembolism (VTE) and postoperative bleeding are important complications of lung resection surgery. We investigated the preventive effect of mechanical prophylaxis versus pharmacological prophylaxis after lobectomy, and evaluated the effect of both on the incidence of hemorrhagic events.

Methods: A prospective study of 424 lobectomies with moderate to high risk of VTE (Caprini risk score <5) in a single center was performed from April 2020 to March 2021. Patients were 1:1 randomly allocated to mechanical prophylaxis or to the low-molecular-weight heparin (LMWH)-combination-prophylaxis. The incidence of postoperative thrombotic and bleeding events and relevant factors of the two groups were analyzed.

Results: A total of 410 participants, with 202 and 208 in the mechanical prophylaxis and LMWH-combination-prophylaxis groups respectively, were selected for analysis. Both groups had similar baseline and clinical characteristics. There were no cases of VTE or major bleeding during the study, but the incidence rate of minor bleeding in the LMWH-combination-prophylaxis group was significantly higher than mechanical prophylaxis group [odds ratio (OR) 0.035, 95% confidence interval (CI): 0.011–0.113].

Conclusions: A case-by-case risk assessment of VTE and hemorrhage remains necessary to determine the most appropriate method of thrombosis prophylaxis for patients undergoing pulmonary surgery. Mechanical prophylaxis may be preferable for lung cancer patients with moderate to high risk of VTE (Caprini risk score <5) undergoing lobectomy.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100051073.

Keywords: Bleeding events; prophylaxis; lung cancer; postoperative; venous thromboembolism (VTE)

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Introduction

Venous thromboembolism (VTE), consisting of deep vein thrombus (DVT) and subsequent pulmonary embolism (PE), is a common complication in patients undergoing lung cancer surgery (1-3). Although the frequency of PE is low, it is the most common preventable cause of death

among patients hospitalized for surgery (4-6). The absolute risk of VTE depends on multiple factors (7), including surgery, cancer and immobilization. One of the most important being surgical intervention, especially for lung cancer patients undergoing major surgery, because the main pathogenic factors of VTE, such as vascular wall damage, hypercoagulable state and venous stasis, may be promoted during surgery (8). It is essential to prevent VTE in patients following pulmonary lobectomy.

Methods to prevent VTE include mechanical prophylaxis, which usually uses intermittent pneumatic compression (IPC) and medical elastic stockings (MES), and pharmacological prophylaxis such as low-molecular-weight heparin (LMWH). In Western countries, both mechanical and pharmacological prophylaxis are widely used as standard preventive methods for VTE after routine surgery (9-11). Widespread overuse of LMWH is likely to translate into a risk of adverse events, including bleeding events. Although rare in the literature, intrathoracic hemorrhage in the early postoperative period is another worrying complication and the most common indication for early reoperation, and serious cases can lead to the patient's death. A recent study described bleeding in 2.1% of patients after lobectomy, leading to reoperation in 1.4% of patients (12). There are differences in the risk of VTE between different races, Asians are considered to have a lower risk of VTE (13). The Caprini tool (14) is an effective, simple, economical and practical VTE risk assessment model, which is a validated risk assessment model used primarily in the USA. Most guidelines classify hospitalized patients with active cancer based on the Caprini risk scale, especially those undergoing surgery. Current guidelines promote that according to the Caprini risk scale, pharmacological prophylaxis with unfractionated heparin or LMWH should be given 2–12 h prior surgery and within 6–12 h after surgery in critically ill (≥5 points) patients (15,16). Mechanical prophylaxis or pharmacological prophylaxis are performed in moderate (2 points) and high risk (3 or 4 points) patients, but there is no standardization on which method is more recommended. It depends on the expertise of the attending physician or surgeon, especially for the Chinese population. According to a survey of thoracic surgery in China, 66.96% of surgeons recommended thrombosis prophylaxis on the first day after lung cancer resection, and prolonged prevention after discharge. Half of the surgeons admitted that their decision on the method and duration of prophylaxis was based on their clinical experience (17). Therefore, there is an urgent need for research to provide evidence for thoracic surgeons to base their decision on the most suitable prevention program for VTE.

We aimed to compare the incidence and risk factors for postoperative VTE and hemorrhage in patients with mid-to-high risk of thrombosis (Caprini risk score <5) following pulmonary lobectomy, and to evaluate the effect of mechanical prophylaxis and pharmacological prophylaxis on the incidence of postoperative thrombotic or bleeding events.

We present the following article in accordance with the CONSORT reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4231).

Methods

Study design and treatment protocol

This prospective study was conducted at the First Affiliated Hospital of Zhejiang University, School of Medicine, which is a tertiary care hospital located in eastern China. The study was approved by Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (approval ID: 2019-1432-1) and registered on the Chinese Clinical Trial Registry website (ChiCTR2100051073). All aspects of the study complied with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of First Affiliated Hospital, Zhejiang University School of Medicine specifically approved that no informed consent was required because all data were going to be analyzed anonymously. We aimed to compare the effects of mechanical prophylaxis combined with pharmacological prophylaxis to that of mechanical prophylaxis for prevention of VTE following pulmonary lobectomy. All the patients eligible for the study underwent surgery performed by a single thoracic surgery team. Simple randomization method was used.

In this two-parallel study, the included patients were 1:1 randomly divided into mechanical prophylaxis group (Group A) and mechanical prophylaxis plus LMWH group (Group B) through a computer-generated random number table and sealed opaque envelope technique was performed for allocation concealment. In groups A and B, mechanical prophylaxis of IPC and MES was implemented immediately before the operation until the patient was fully ambulant as the basic treatment for prevention of VTE. For patients allocated to Group B, 4,000 IU of LMWH (i.e., enoxaparin sodium) was administered as a daily subcutaneous injection from the first postoperative day until discharge. If the

drainage volume exceeded 500 mL/day or a bleeding event occurred, the administration of LMWH was suspended.

The clinical pharmacists participating in this study had collaborated with the thoracic surgery team for at least 1 year and understand the research protocol and intervention methods, responsible for collecting patient information, randomly assigning patients, and evaluating the results.

Patient selection

Patients who were ≥18 years, in good physical condition, and planned to undergo curative pulmonary lobectomy were eligible for this study. The exclusion criteria were: (I) current peptic ulceration, or intracerebral hemorrhage or hemorrhagic transformation; (II) serious renal or liver disease; (III) administration of anticoagulants and/or antiplatelet agents such as aspirin, clopidogrel sulfate, warfarin, etc. before surgery; (IV) high values of D-dimer (>10 μg/mL) within 4 weeks before surgery; (V) Caprini risk score ≥5 points. VTE risk assessment using the Caprini tool assigned the patients to two categories according to their score: moderate (2 points) or high risk (3 or 4 points).

Outcomes

VTE and major bleeding were highly prevalent in patients after lung surgery and can cause severe morbidity. Both of them were associated with an increased risk of death and could be indicators of lung cancer mortality (18). The primary outcome was the incidence of VTE and the incidence of bleeding events. The patient's stable condition and discharge from the hospital was the primary endpoint. VTE included DVT and PE. Patients with a D-dimer value <10 μg/mL and no clinical symptoms suggestive of VTE on the seventh postoperative day were judged to have no VTE (19). Patients with clinical symptoms suggesting VTE or patients with a D-dimer value >10 μg/mL on the seventh postoperative day were assessed for the presence of VTE through invasive examinations such as contrast-enhanced computed tomography (CT) and venography. Adverse events concerning bleeding included major bleeding that required surgical or endoscopic hemostasis or blood transfusion, and minor bleeding that required either discontinuation of drug treatment or drug hemostasis. All results were evaluated on the first, third, and fifth days after surgery, because a previous study found that fluctuations in D-dimer levels were generally significant during the first five days after lung resection (20).

Sample size

Postoperative patients with Caprini risk score <5 can be treated with physical therapy with or without heparin, but there is little literature on whether heparin should be administered to these patients after radical resection of lung cancer. We previously investigated 133 patients in the general thoracic surgery ward and found that those with a Caprini risk score <5 received physical therapy plus heparin, but the postoperative bleeding rate was as much as 32.3%, which seriously affected the prognosis of the patients. Therefore, we planned to reduce the bleeding rate by 15% with physical therapy alone through this clinical trial. Sample size was calculated by PASS version 20.0 (Power Analysis and Sample Size) as follows: the incidence rate of bleeding in Group B was 32.3%, and in Group A was 17.3%, the significance level of both sides was 0.05, and the power was 0.90. Therefore, considering approximately 20% of dropped cases, we set the target number of cases as 424.

Statistical analysis

All data was analyzed using the Statistical Package for Social Sciences (SPSS 20.0) software. We evaluated the baseline clinical variables of age, sex, body mass index (BMI), Caprini risk score, operation time, intraoperative bleeding volume and cancer stage between the two groups. Continuous variables were verified for normal distribution by Kolmogorov-Smirnov test, and then the mean ± SD (standard deviation) or median and range were calculated. Student's *t*-test or non-parametric test was used to compare the difference in continuous variables between groups A and B. For categorical variables, frequency and percentage were performed and the χ^2 test was used to compare the differences between different groups. To assess the incidence of minor bleeding after surgery, including drainage bleeding, gastrointestinal bleeding/hemoptysis and other bleeding diagnosed, we estimated the binomial ratio and 95% confidence interval (CI) of minor bleeding in the two groups. In addition, in order to compare the incidence of minor bleeding between the two groups, the odds ratio (OR) was calculated with a 95% CI: based on the exact confidence limit.

Results

Patients' characteristics and populations analysis

From April 2020 to March 2021, 424 patients were

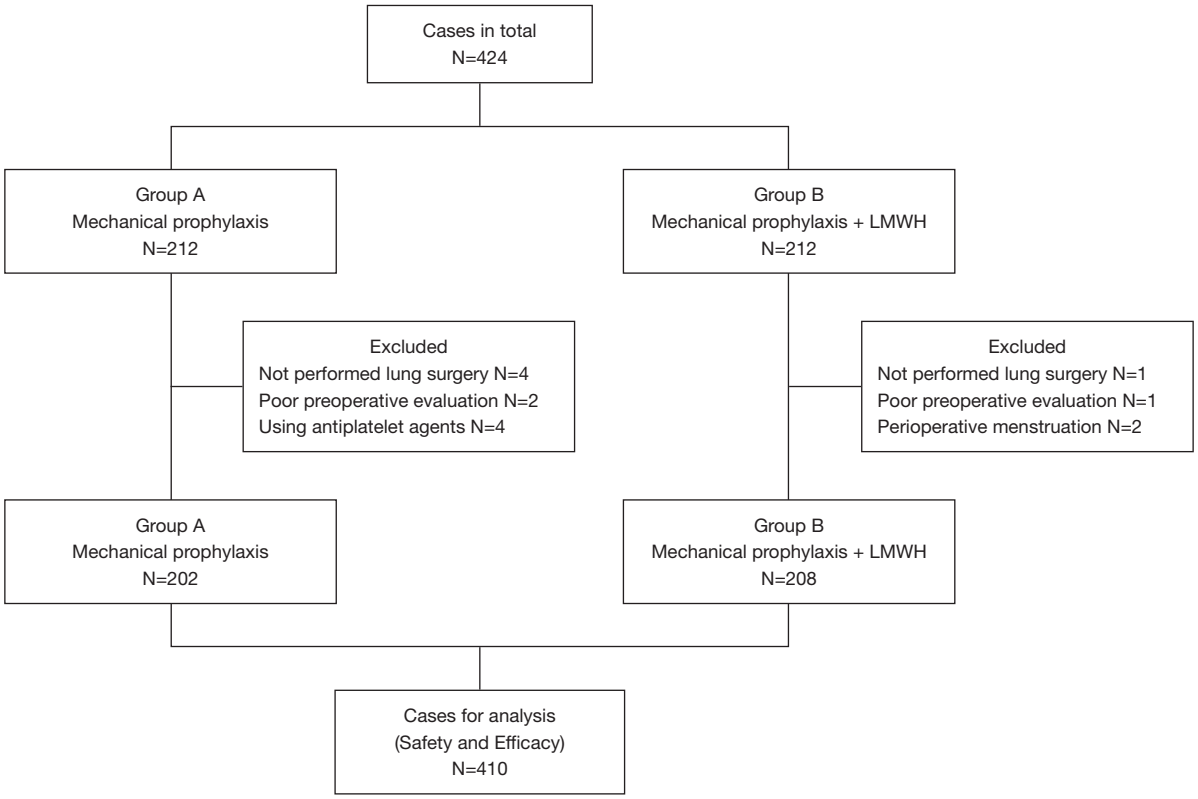

Figure 1 Flow chart of study design and patient selection. LMWH, low-molecular-weight heparin.

recruited, and randomly divided into Group A and Group B, with 212 cases in each group; five patients were excluded for not undergoing pulmonary lobectomy, and another nine patients were excluded because of poor evaluation of preoperative thrombosis, administration of antiplatelet agents, and perioperative menstruation. Therefore, a total of 410 participants (202 patients in Group A, 208 patients in Group B) were used for analysis. The flowchart is shown in *Figure 1*.

The baseline characteristics of the two groups were comparable (*Table 1*). We found that among the 410 patients, 90.2% (370/410) had early lung cancer (stage I). The median age was 56 years, and 61.95% (254/410) were female. Other characteristics, including BMI, operation time, and intraoperative bleeding volume, of the two groups are listed in *Table 1*. The demographic and background characteristics of the patients were unbiased, and the clinical characteristics of the two groups were not significantly different.

Outcome measures

Other than the three patients in Group A who had abnormally elevated D-dimer levels, none of the patients had any VTEs during the study period, and there was no significant difference between the two groups. One of the three patients was a 43-year-old woman who was diagnosed as early lung cancer (stage I), with an operation time of 105 min and intraoperative bleeding volume of 50 mL. Her D-dimer rose to 5.13 μg/mL on the fifth postoperative day. Considering that she had no other high-risk factors, she did not receive LMWH treatment, and D-dimer fell below 2,000 after 1 week. The other two patients were both male with mid-stage lung cancer (stage II), and subsequently were administered LMWH. A 66-year-old male patient underwent left upper lobectomy with operation time of 174 min and intraoperative bleeding volume of 300 mL. His D-dimer rose to 8.72 μg/mL on the first postoperative days and as the patient was still on bed rest, LMWH treatment was given. On the seventh day after the operation, D-dimer increased to 12.23 μg/mL and then showed a downward trend. Because the chest drainage tube was not removed, the patient was treated with LMWH for 17 days until discharge. The other patient was a 59-year-old male patient with adenocarcinoma who underwent right lower

Table 1 Patients' baseline and clinical characteristics

Characteristic	Group A (n=202)	Group B (n=208)	Z or χ^2	P value
Age, years, median [range]	56 [18–72]	56 [19–74]	0.249	0.804
Sex			0.190	0.663
Male, n (%)	79 (39.1)	77 (37.0)		
Female, n (%)	123 (60.9)	131 (63.0)		
BMI, kg/m^2, median [range]	22.4 [17.1–28.0]	22.4 [15.6–29.1]	0.151	0.880
Caprini risk score, n (%)			0.146	0.702
Moderate (2 points)	20 (9.9)	23 (11.1)		
High (3 or 4 points)	182 (90.1)	185 (88.9)		
Cancer stage, n (%)			0.055	0.814
Stage I	183 (90.6)	187 (89.9)		
Stage II	19 (9.4)	21 (10.1)		
Operation time, min, median [range]	109 [52–255]	109 [46–279]	0.144	0.886
Bleeding volume, mL, median [range]	50 [10–300]	50 [10–400]	0.814	0.416

Group A: mechanical prophylaxis; Group B: mechanical plus LMWH. BMI, body mass index; LMWH, low-molecular-weight heparin.

Table 2 Incidence of bleeding events in full analysis

Event	Group A (n=202)		Group B (n=208)		OR	95% CI
	n	Frequency, %	n	Frequency, %		
Major bleeding, n (%)	0	0.0	0	0.0	–	–
Minor bleeding, n (%)	3	1.5	63	30.3	0.035	0.011–0.113
Drainage bleeding	2	1.0	24	11.5	–	–
Gastrointestinal bleeding/hemoptysis	1	0.5	38	18.3	–	–
Other bleeding	0	0.0	1	0.5	–	–

Group A: mechanical prophylaxis; Group B: mechanical plus LMWH. OR, odds ratio; CI, confidence interval; LMWH, low-molecular-weight heparin.

lobe resection with an operation time of 255 min and intraoperative bleeding volume of 200 mL. His D-dimer rose to 9.21 μg/mL on the third postoperative day and he was administered daily LMWH injections. After six days, the patient's D-dimer level was essentially normal and he was discharged.

Due to no clinical symptoms or CT results that indicated VTE, these three patients were judged to not have VTE. Two patients recovered successfully and were discharged early, while the third patient was discharged after removal of the thoracic drainage tube.

We also examined the risk of bleeding events (*Table 2*). The incidence of major and minor bleeding was compared between the two groups. Among the 410 patients, no major bleeding events were confirmed before discharge. There were three cases (1.5%, 95% CI: 0.2–3.2%) in Group A and 63 cases (30.3%, 95% CI: 24.0–36.6%) in Group B of minor bleeding. The incidence rate of minor bleeding in the LMWH group was obviously higher than that in the non-LMWH group (OR 0.035, 95% CI: 0.011–0.113). The minor bleeding adverse events in Group A versus Group B were drainage bleeding (1.0% *vs.* 11.5%, respectively; P<0.001), gastrointestinal bleeding/hemoptysis (0.5% *vs.* 18.3%, respectively; P<0.001), other bleeding (0% *vs.* 0.5%, respectively; P=0.323). In the Group B, administration of LMWH was ceased when bleeding events occurred, and none

of these patients developed VTE. In addition, two patients in Group B also ceased LMWH administration when the postoperative drainage volume exceeded 500 mL/day.

Discussion

The general incidence of VTE is reported to be 0.2–20% after lung resection, owing to the varying choice of pharmacological and mechanical thromboprophylaxis (8). Studies have reported a variety of potential patient and procedural risk factors, including: older age, obesity, tumor type, disease stage, recent surgery, scope of resection, operative duration, and postoperative bed rest (21). The combination of lung cancer and surgical procedure constitutes a higher risk of VTE in patients, especially in the first month after surgery (22). The prognosis of hospitalized lung cancer patients may worsen after development of VTE, indicating that such surgical patients should be carefully monitored for it (23). Our study revealed that participants in both groups had similar baseline and clinical characteristics, including age, sex, BMI, cancer stage, operation time, and intraoperative bleeding volume. Compared with the mechanical prophylaxis group, receiving LMWH treatment during the perioperative period the potential to lower the risk of VTE, but there was no statistical difference. Some researchers report that early ambulation facilitated by epidural analgesia may be associated with a lower incidence of DVT (24). There were no cases of VTE in the study patients, likely due to almost all of them receiving epidural analgesia.

Some guidelines recommend that for patients with a higher risk of major bleeding (including those undergoing expanded pulmonary resection), the time of thrombosis prophylaxis should be delayed, and mechanical prophylaxis should be preferred (25). In order to identify DVT and PE early in the prevention process, continuous monitoring of positive symptoms and blood markers as well as clinically related risks is required (26). As the final product of fibrin degradation, D-dimer is a powerful indicator of VTE and has been reported as a prognostic marker for lung cancer (27-29). When cancer patients undergo surgery, the level of D-dimer will fluctuate. Studies have shown that D-dimer levels were higher than baseline in patients who developed VTE after surgery and affected the survival of patients. High D-dimer level predicts poor survival and early recurrence (30). Combining the clinical risk factors to assess the dynamic changes of D-dimer can help surgeons better manage patients and identify the occurrence of postoperative thrombotic events. Because many clinical cases are asymptomatic when thrombosis occurs, effective surveillance of coagulation indicators is particularly important. In this study, we paid more attention to the changes in D-dimer levels before surgery and on the first, third, and fifth day after surgery, and observed that three patients in the mechanical prophylaxis group had a significant change in their D-dimer levels. One of them recovered spontaneously, and the other two were administered LMWH on the second and third day after surgery. In clinical practice, patients who are highly suspected of VTE based on D-dimer results or related symptoms require further examination. DVT is mainly diagnosed by ultrasound whereas PE is confirmed by pulmonary angiography or computer tomography pulmonary angiography (CTPA). Through close monitoring and active treatment by clinical pharmacists and clinicians, none of these three patients developed VTE, their D-dimer levels gradually restored to normal and they were discharged uneventfully.

Early postoperative bleeding is also a relevant complication following pulmonary lobectomy, and improper handling may potentially lead to death. According to reports, the postoperative bleeding rate is 2–3% (12). Postoperative bleeding is related to some factors such as cardiovascular disease, neoadjuvant radiotherapy, surgical methods, and mediastinal lymph node dissection (31). Compared with video-assisted thoracoscopic surgery (VATS), open approach was significantly associated with postoperative bleeding, which probably because VATS patients usually composed of selected groups with more peripheral, smaller and safer resection lesions (32). There seems to be no statistically significant association between prevention time and thrombosis or bleeding (8). In our study, no major bleeding occurred in either the mechanical prophylaxis group or the LMWH plus mechanical prophylaxis group, which may be related to the early stage of lung cancer. However, LMWH administration was found to be significantly associated with postoperative bleeding. In this study, the incidence of minor bleeding in the LMWH plus mechanical prophylaxis group was significantly higher than that in the mechanical prophylaxis group (30.3% *vs.* 1.5%, respectively; $P<0.001$). All patients with minor bleeding in the LMWH group ceased LMWH administration and continued with mechanical prophylaxis only, and no cases of VTE occurred; however, 5% of patients required further treatments. These findings should be taken into consideration when deciding on pharmacological prophylaxis. Therefore, for patients with

moderate to high risk of VTE undergoing thoracic surgery, use of LMWH can be delayed. Mechanical prophylaxis is recommended, and IPC is best used.

This study has some limitations. First of all, the focus was on early VTE prophylaxis in patients after lobectomy (up to discharge), and mid- to long-term VTE prophylaxis was not evaluated. Therefore, it may underestimate the true incidence of VTE. Secondly, the postoperative blood test was performed around 7 o'clock in the morning, but this is not a specific time point from the perspective of LMWH administration. In addition, the study group comprised a very specific cohort of Chinese patients, and mainly explored the situation of early-stage lung cancer patients. Thus, these results can be applied to individuals with similar pathologic and oncologic status, but whether they can be expanded to other races remains to be further studied.

Conclusions

VTE and postoperative bleedings are two relevant complications following lung surgery. This study showed that compared with the LMWH plus mechanical prophylaxis group, the mechanical prophylaxis group did not show increased risk of VTE among patients undergoing lobectomy with a moderate to high risk of VTE (Caprini risk score <5), but the risk of minor bleeding was significantly reduced. In order to determine the most appropriate method of thrombosis prophylaxis, a case-by-case risk assessment of VTE and bleeding is still required. In this trial, we also found that the incidence of VTE in Chinese patients was much lower than expected. Mechanical prophylaxis, especially IPC, may be preferable for patients with moderate to high risk of VTE undergoing lung surgery.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-4231

Trial Protocol: Available at https://dx.doi.org/10.21037/atm-21-4231

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-4231

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-4231). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine (approval ID: 2019-1432-1), and all aspects of the study complied with the Declaration of Helsinki (as revised in 2013). The Ethics Committee of First Affiliated Hospital, Zhejiang University School of Medicine specifically approved that no informed consent was required because all data were going to be analyzed anonymously.

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