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Subclinical venous thromboembolism after pulmonary resection for lung cancer: an observational study

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Abstract

Background Subclinical venous thromboembolism is a hidden pathology which may present with catastrophic consequences if not diagnosed at an early stage. This study was undertaken to estimate the occurrence and associated risk factors of subclinical deep vein thrombosis after lung resection for lung cancer patients. A prospective observational cohort study was performed in a tertiary cardiothoracic surgery center. One hundred fifty patients who underwent different types of lung resection for lung cancer were enrolled. Caprini's risk score was assessed in all patients. All patients received prophylactic stockings and anticoagulants. On the 5th postoperative day, a duplex venous ultrasound of bilateral lower limbs was performed on every asymptomatic patient.

Results Out of 150 patients enrolled in the study, 147 patients completed the study. Four patients (2.72%) developed subclinical deep vein thrombosis. The patients were divided into 2 groups: group 1 ($n=143$) post-lung resection and no DVT and group 2 ($n=4$) with post-lung resection subclinical DVT. No patient developed postoperative clinical DVT. The incidence was found to be highest in the group of individuals who had a longer stay in the ICU (odds ratio 37.9) ($p=0.04$). Among the various pathologies, the incidence was higher in patients who received preoperative chemotherapy (odds ratio 21.9) ($p=0.001$). One patient in the subclinical DVT group (25%) died, while no mortality was observed in the no DVT group.

Conclusions The incidence of subclinical deep vein thrombosis is low in the postoperative period among patients undergoing lung resection for lung cancer if appropriate prophylactic measures are applied. However, patients receiving preoperative chemotherapy and those with longer periods of immobilization are at a higher risk of developing postoperative DVT despite anticoagulant prophylaxis. Due to the sample size and design limitations, the mentioned risk factors could be associated with DVT not a cause of DVT. It might be justified to screen these high-risk groups to detect subclinical DVT to allow for post-discharge prophylaxis.

Keywords Thromboembolism, Lung cancer, Subclinical

Background

Deep venous thrombosis (DVT) in post-surgical patients is not uncommon in lung cancer patients undergoing resection. The combination of malignancy, surgical trauma, chemotherapy, and smoking are all synergistic factors raising the risk. Most of the patients developing postoperative DVT are subclinical and asymptomatic; however, its complications like pulmonary embolism carry a very considerable mortality rate [1, 2]; hence,

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prevention of DVT assumes paramount importance. Other complications, resulting from incompetent or destroyed valves, include chronic venous insufficiency with subsequent development of varicose veins in about 60% of patients [3], lipodermatosclerosis, and venous ulcers causing considerable disability, the incidence being as low as 0–6.5% [4–6].

Subclinical DVT is a condition of the presence of thrombus within flowing blood in the deep veins without any clinical features. Complications of DVT can be prevented more successfully when detected in its subclinical phase rather than after the development of clinical signs and symptoms. Although there is a large body of research describing the incidence of VTE following orthopedic, neurosurgical, gynecological, and cardiovascular surgery, there has been minimal research describing the incidence and risks associated with the occurrence of subclinical deep vein thrombosis after lung resection surgeries [7–12].

The present study was undertaken to estimate the occurrence and associated risk factors of subclinical deep vein thrombosis at our institute after lung resection for lung cancer patients in the elective and urgent setting.

Methods

This single tertiary center prospective observational study was carried out on 150 patients who had undergone lung resection for lung cancer. To include the required sample size, the study was conducted for a 21-month period commencing July 2020 and ending March 2022.

The study included all patients with resectable non-small cell lung cancer and patients requiring lung resection for metastatectomy. Preoperative diagnosis was based on CT chest, PET CT, and tissue diagnosis which was performed according to tumor position (CT guided biopsy, bronchoscopy, endobronchial ultrasound (EBUS), and esophageal ultrasound EUS). Decision of resection was based on MDT discussion. The study included adult patients undergoing elective lung resection, including lobectomy, bi-lobectomy, pneumonectomy wedge resection, segmentectomy, metastasectomy, open thoracotomy, or video-assisted thoracoscopic surgery (VATS), while pediatric group (< 18 years old), pregnant females, and patients with signs and symptoms of DVT (preoperative) were excluded from the study.

Enrolment procedure

Each participant was enrolled in the study after the informed consent process had been completed and the participant met all the inclusion criteria and none of the exclusion criteria. Participants were allowed to withdraw their data from the research process at any time.

Ethical considerations

Participants were given fully informed consent to participate in the study. These informed consents in this prospective study were written and verbal consents. Participant confidentiality and data security were guaranteed. Participants were able to withdraw from the research process at any time, were also able to withdraw their data if it was identifiable as theirs, and were told when this would no longer be possible. Any expected benefits or potential harm to the research participant were thoroughly discussed.

The Ain Shams University ethical committee approved the study (FMASU MD 130/2020).

Study procedures

This study was conducted on 150 patients who had lung cancer and underwent lung resection surgery (wedge resection, segmentectomy, lobectomy, or pneumonectomy). Patients were investigated by venous Doppler on both lower limbs below and above the knee on postoperative day 4 or just before hospital discharge if hospital stay < 4 days to pick up subclinical VTE. The patients were administered prophylactic low molecular weight heparin postoperatively.

Study procedure risks

We anticipate minimal additional risks by undertaking the study. The venous Doppler study on both lower limbs has no risks for the patients.

Adverse event

An adverse event is any untoward medical occurrence that results in the following: significant pulmonary complications, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, any condition requiring medical or surgical intervention, and death. An adverse event can therefore be any unfavorable or unintended sign, symptom, condition, and/or observation that may or may not be related to the study treatment.

Operative and postoperative management

All patients were operated on via post-lateral thoracotomy or through video-assisted thoracoscopy (VATS).

All patients wore compression elastic socks before and during the surgery and were extubated in the OR. All the patients were kept in the postoperative intensive care unit for at least one night. Every day, patients were encouraged to cough, participate in respiratory physiotherapy, and use an incentive spirometer by the respiratory physiotherapist. If there were no contraindications, the patients were returned to the thoracic

surgical unit the next day and encouraged to walk around as quickly as possible after giving good analgesia. According to Caprini's Risk Assessment for Surgical Patients, all patients received prophylactic anticoagulation against VTE enoxaparin sodium (R/Clexane) subcutaneous injection at a dose of 1/2 mg/kg on the next morning of surgery after excluding any postoperative bleeding complications. This was continued daily until hospital discharge. On postoperative day 4 or before discharge to home if hospital stay < 4 days, all patients had bilateral lower limb venous Doppler done, were asked about symptoms, and examined for signs of VTE. Patients with subclinical venous thromboembolism were discharged on a 3-month course of anticoagulation and reviewed every 2 weeks, with questions concerning VTE signs and symptoms and a Doppler examination.

Parameters measured and recorded

(a) Preoperative parameters: patient demographics; age, sex, BMI, risk factors, primary pathology, laterality, Caprini's Risk Assessment, and elastic stocking on admission
(b) Intra-operative parameters: type of procedure, elastic stocking, surgical technique, time of operation (long operation time if > 3 h) and extubate patients on the table.
(c) Postoperative parameters: Prophylactic anticoagulation for all patients, early mobilizations, spirometer, good analgesia, and bilateral lower limb venous Doppler on day 4 or just before hospital discharge if hospital stay < 4 days.

Statistical analysis

Data were collected, revised, coded, and entered into IBM SPSS version 23. The quantitative data were presented as median, standard deviations, and ranges when parametric. The data for qualitative variables was presented in the form of numbers and percentages. The chi-square test and/or Fisher exact test were used to compare groups regarding qualitative data if the expected count in any cell was less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using an independent *t*-test while non-parametric data were done by using the Mann–Whitney test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered a significant *p*-value < 0.05. Binary logistic regression analysis was used for calculating the highest risk factors for developing post-lung resection DVT.

Results

Over the study period, a total of 150 patients were screened, and three patients were excluded from the study due to their inability to perform Doppler US. One of them had elephantiasis, and the remaining two patients had previous operations in the lower limb. So, the total number of studied patients was 147. All patients were asymptomatic regarding lower limb DVT symptoms after lung resection. According to the results of Doppler US, the patients were divided into 2 groups: group 1 ($n=143$) with post-lung resection and no DVT and group 2 ($n=4$) with post-lung resection subclinical DVT.

The incidence of patients who developed subclinical DVT was 2.721%.

Of patients with subclinical DVT ($n=4$), one died owing to multiorgan failure, and the other three were discharged to home on oral anticoagulants for 3 months After excluding signs and symptoms of VTE, a Doppler ultrasound revealed remission of DVT.

Patient demographics

The median age of the patients studied in group 1 ($n=143$) was 55 years, ranging between 18 and 78 years. Of cases, 57.3% were male, while it was 48 years in group 2 ($n=4$), ranging between 40 and 63 years. Half of the cases were male, 50%. The median BMI in group 1 ($n=143$) was 30.8, while it was 34.6 in group 2 ($n=4$). There was a statistically insignificant difference between both groups as regards patient demographics (Table 1).

As regards Caprini risk assessment, there were 112 patients (78.3%) with moderate Caprini VTE Risk in group 1 ($n=143$) versus 1 patient (25%) in group 2 ($n=4$). There were 31 patients (21.7%) with high Caprini VTE Risk in group 1 ($n=143$) versus 3 patients (75%) in group 2 ($n=4$). There was a statistically significant difference between both groups (*P*-value 0.01) (Table 2).

As regards age, in group 1 ($n=143$), 50 patients were over the age of 60 (35%), while only 1 patient (25%) in group 2 ($n=4$) was over the age of 60 at the time of the study (*P*-value = 0.68) (Table 3).

In group 1 ($n=143$), 78 patients (54.5%) were smokers, while three out of four patients (75%) in group 2 ($n=4$) were smokers (*P*-value = 0.41).

Diabetic patients in group 1 ($n=143$) were 26 patients (18%), while in group 2 ($n=4$), there were 2 patients (50%) (*P*-value = 0.11).

As regards the history of stroke, only 2 patients out of 143 patients (1.4%) in group 1 had a history of stroke, while none of the 4 patients (0%) in group 2 had. *P*-value = 0.81.

As regards history of chemotherapy, in group 1 ($n=143$), only 4 patients (2.8%) had previously

Table 1 Description of personal data among the 2 groups

		Group		*P*-value
		Group 1 = No DVT group (n = 143)	***Group 2 = DVT group (n = 4)***	
Sex	Male	82 57.3%	2 50%	0.77
Age (year): median (range)		55 (18–78)	48 (40–63)	0.62
Height (cm): median (range)		166 (145–191)	159.50 (158–170)	0.89
Weight (kg): median (range)		85 (42–118)	87.5 (85–90)	0.66
BMI median (range)		30.8 (18.5–43.7)	34.6 (29.4–35.6)	0.6

Table 2 Caprini's VTE Risk Assessment for the studied patients

		Group		*P*-value
		Group 1 = No DVT group (n = 143)	***Group 2 = DVT group (n = 4)***	
Caprini VTE risk assessment	Moderate	112 78.3%	1 25%	0.01
	High	31 21.7%	3 75%	

Table 3 Preoperative risk factors characteristics of the studied patients

		Group		*P*-value
		Group 1 = No DVT group (n = 143)	***Group 2 = DVT group (n = 4)***	
Old age	Yes	50 35%	1 25%	0.68
Morbid obesity	Yes	25 17.5%	0 0.0%	0.35
Diabetic	Yes	26 18.2%	2 50%	0.11
Smoker	Yes	78 54.5%	3 75%	0.41
Previous stroke	Yes	2 1.4%	0 0.0%	0.81
Another tumor	Yes	4 2.8%	2 50%	0.001
Previous chemotherapy	Yes	4 2.8%	2 50%	0.001

received chemotherapy, whereas 2 patients out of 4 patients (50%) in group 2 had previously received chemotherapy (one had metastatic colorectal cancer and the other had metastatic breast cancer). There was a statistically significant difference between both groups (*P*-value = 0.001).

In terms of preoperative diagnosis, 114 patients (79.9%) in group 1 ($n = 143$) were diagnosed with bronchogenic carcinoma, 25 cases (17.5%) with carcinoid tumors, and 4 cases (2.8%) with a history of previous tumors other than the lung. Two cases (50%) in group 2 ($n = 4$) were diagnosed with bronchogenic carcinoma, and two patients (50%) had a history of previous tumors, one with colorectal cancer, and the other with breast cancer. There was a statistically significant difference between both groups (*P*-value = 0.001) (Table 4).

In terms of postoperative morbidity and mortality, in group 1 ($n = 143$), 7 patients (4.9%) developed postoperative arrhythmias, 4 patients (2.8%) had superficial wound infections, 12 patients (8.4%) complained of prolonged air leak lasting more than 5 days, 7 patients (4.9%) developed lobar lung collapse necessitating fibro optic bronchoscopy, 4 patients (2.8%) experienced postoperative bleeding affecting hemodynamics necessitating re-exploration, and 36 patients (25.2%) experienced post-thoracotomy pain (> 5 on visual analogue score). In this group, there was no hospital mortality. Patients reexplored for bleeding started receiving enoxaparin sodium on postoperative day 2 instead of day 1 (see Table 5).

In group 2 ($n = 4$), two patients (50%) experienced atrial fibrillation in the intensive care unit (ICU), had persistent air leaks lasting more than 5 days, and developed lung atelectasis; one required fibro optic bronchoscopy; and two developed postoperative thoracotomy pain. In this group, there was one death (25%) due to a lengthy ICU stay of more than 58 days (this patient experienced a cerebrospinal fluid (CSF) leak during surgery, which was complicated by stroke, empyema, persistent air leak, and lung collapse requiring fibro optic bronchoscopy, and eventually died due to multiorgan failure). The cause of death was not related to developing DVT but rather DVT seems to be associated with his prolonged stay (see Table 5).

Table 4 Intra-operative variables

		Group		*P*-value
		Group 1 = No DVT group (n = 143)	***Group 2 = DVT group (n = 4)***	
Diagnosis	Bronchogenic carcinoma	114 79.7%	2 50%	0.001
	Carcinoid tumor	25 17.5%	0 0.0%	
	Metastasis	4 2.8%	2 50%	
Operation	Right upper lobectomy	19 13.3%	2 50%	0.002
	Right lower lobectomy	33 23.1%	0 0.0%	
	Left upper lobectomy	19 13.3%	0 0.0%	
	Left lower lobectomy	35 24.5%	0 0.0%	
	Pneumenectomy	4 2.8%	0 0.0%	
	VATS lobectomy	8 5.6%	0 0.0%	
	Metastatectomy	5 3.5%	2 50%	
	Sleeve lobectomy	14 9.8%	0 0.0%	
	Bi-lobectomy	6 4.2%	0 0.0%	
Long Operation Time > 3 h	Yes	18 12.6%	1 25%	0.46

Table 5 Postoperative morbidity and mortality

		Group		*P*-value
		Group 1 = No DVT group (n = 143)	***Group 2 = DVT group (n = 4)***	
Arrhythmia	Yes	7 4.9%	2 50%	0.001
Wound infection	Yes	4 2.8%	1 25%	0.01
Prolonged air leak > 5 days	Yes	12 8.4%	2 50%	0.005
Atelectasis	Yes	14 9.8%	2 50%	0.01
Lobar collapse for bronchoscopy	Yes	7 4.9%	1 25%	0.08
Reoperation for bleeding	Yes	4 2.8%	0 0.0%	0.73
Pain (more than 5 on VAS)	Yes	36 25.2%	2 50%	0.26
Empyema	Yes	2 1.4%	1 25%	0.001
Mortality	Yes	0 0.0%	1 25%	0.001

Table 6 Hospital and ICU stay

	Group		*P*-value
	Group 1 = No DVT group (n = 143)	*Group 2 = DVT group (n = 4)*	
ICU stay (days): median (range)	1 (1–4)	2.5 (2–58)	0.04
Hospital stays (days): median (range)	6 (5–14)	8 (6–60)	0.27

Table 7 Binary logistic regression analysis

Risk factors		Score (odds ratio)	*P*-value
	Sex	.07	0.77
	Age	.06	0.79
	Height	.68	0.40
	Weight	.25	0.61
	Old age	.15	0.69
	morbid obesity	.85	0.35
	Caprini VTE risk assessment	6.45	0.01
	Diabetic	2.52	0.11
	Previous chemotherapy	21.97	0.00
	Smoker	.67	0.41
	Previous stroke	.05	0.81
Postoperative	Long operation time > 3 h	.52	0.47
	Arrhythmia	13.66	0.001
	Wound infection	5.78	0.01
	Prolonged air leak > 5 days	7.74	0.001
	Atelectasis	6.42	0.01
	Lobar collapse for bronchoscopy	3.02	0.08
	Reoperation for bleeding	.11	0.73
	Pain	1.22	0.26
	Empyema	10.75	0.001
	Icu stay	37.96	0.001

As regards ICU stay of the studied patients, the median ICU stay in group 1 ($n = 143$) was 1 day, while it was 2.5 days in group 2 ($n = 4$), so there was a statistically significant difference between both groups p-value 0.04. There was a statistically insignificant difference between both groups as regards hospital stay. The median hospital stay in group 1 ($n = 143$) was 6 days, while the median hospital stay was 8 days in group 2 ($n = 4$) (P-value 0.27) (see Table 6).

Using the binary logistic regression analysis for calculating the highest risk factors for developing post-lung resection DVT, preoperative chemotherapy (21.97% higher risk), and prolonged ICU stay (37.96% higher risk) were the highest risk factors for developing subclinical DVT (Table 7).

Discussion

To the best of our knowledge, this is the first study examining the incidence and impact of subclinical DVT after lung resection. The danger of pulmonary embolism is significant, with 80% of PEs occurring without symptoms and two-thirds of deaths happening within 30 min [13]. This concern led NICE to issue guidelines for VTE prophylaxis. However, retrospective medical record reviews and a UK Parliamentary Report have shown that these guidelines are often not followed [13, 14].

One of the main challenges in VTE prophylaxis implementation is translating evidence into practice. The risk of developing DVT varies based on the type of surgery and patient-specific risk factors [14]. Many patients undergoing thoracic surgery are often in poor health and immobile. Those with malignancies face lengthy procedures and significant pressure on large veins, which, combined with increased coagulation activation, elevates the VTE risk [15].

In primary lung cancer, especially adenocarcinoma, factors can disrupt fibrin deposition and breakdown. Tumor cell pro-coagulants, such as tissue factor and cancer pro-coagulant, have been identified in human lung cancer [16]. Adenocarcinoma is also known to cause migratory thrombophlebitis (Trousseau's syndrome) related to the sialic acid moiety in mucin that activates platelets and Factor X [17, 18].

Intraoperatively, procedures like pneumonectomy and lobectomy involve more time and greater tissue manipulation and blood loss, leading to a higher risk of venous thrombosis compared to wedge resection or segmentectomy. Pneumonectomy, in particular, has a higher VTE risk than lobectomy for stage I and II lung cancer due to greater coagulation cascade activation, especially from the seventh postoperative day [19]. Thus, special attention to VTE prophylaxis is crucial in thoracic surgery settings. Postoperatively, the VTE risk increases due to patients' advanced age and higher likelihood of neoplastic diseases as the reason for surgery [20].

Epidural analgesia in thoracic surgery, particularly for lengthy operations, serves as an additional prophylactic measure against VTE [21]. It is essential to advise on the consequences of incorrect prophylaxis use. While there is no shortage of guidelines for VTE prophylaxis, proper monitoring of their implementation is lacking. Over twenty international guidelines advocate for adding VTE prophylaxis in high-risk surgical patients [22].

The American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis guidelines (9th edition) recommend LMWH, UFH, or intermittent

pneumatic pressure stockings for patients with intermediate thrombotic risk. For those with high thrombotic risk but low bleeding risk, the guidelines suggest LMWH, UFH, and mechanical measures, such as elastic stockings or intermittent pneumatic pressure stockings. Mechanical measures, preferably intermittent compression systems, are recommended for patients with a high risk of bleeding until pharmacological prophylaxis can be initiated [23].

Gould et al. recommend LMWH for thoracic surgery patients at high VTE risk but without perioperative bleeding risk (Grade 1B recommendation). They also suggest adding mechanical prophylaxis with elastic stockings (ES) or intermittent pneumatic compression (IPC) to pharmacologic prophylaxis when possible (Grade 2C recommendation) [23]. For patients at high risk for major bleeding, they recommend using mechanical prophylaxis, especially IPC, over no prophylaxis until the bleeding risk is reduced, allowing for the initiation of pharmacologic prophylaxis (Grade 2C recommendation) [23].

Malato and colleagues performed a meta-analysis on 1783 patients studying the impact of DVT in critical patients on hospital stay. DVT patients had longer ICU and hospital stays compared to those without DVT (7.28 days; 95% CI, 1.4–13.15; and 11.2 days; 95% CI, 3.82–18.63 days, respectively). The duration of mechanical ventilation was significantly increased in DVT patients (weighted mean difference, 4.85 days; 95% CI, 2.07–7.63). They concluded that DVT significantly affects clinical outcomes and cost [24].

Doppler ultrasound screening for subclinical DVT is a valuable and safe tool for postoperative patients. In a study by Swanson, Doppler ultrasound screening was offered to 100 consecutive outpatients undergoing a variety of cosmetic plastic surgeries. Compression, color Doppler imaging, and Doppler waveform analyses were used to analyze the deep veins of the lower extremities, including the calf veins. Ultrasonography was used to evaluate twenty-five control participants who did not undergo surgery. A survey was administered to all participants after the scans. He concluded that Doppler ultrasound imaging of the lower extremities is a valuable, noninvasive method for detecting deep venous thromboses in plastic surgery outpatients. [25].

Interestingly, the results of this study may have different impacts on clinical practice in different regions, as Asians claim a lower incidence of postoperative thromboembolism postoperatively and do not administer routine prophylactic anticoagulants [26].

The role of the Caprini RAM in surgery for resection of cancer lung may be limited since most patients (up to 99%) have moderate [5–8] to high (≥9) Caprini scores. While a tailored approach to VTE chemoprophylaxis based on the patient's Caprini score is effective, there are risk factors specific to lung cancer patients that are not accounted for within the Caprini model. Further research into a specific risk stratification model tailored to thoracic surgery patients may, therefore, be of use to identify patients at greatest risk of VTE and most benefit from extended thromboprophylaxis.

Limitations of our study include heterogeneity of the type of surgical resection performed although theoretically, this should not influence the incidence of subclinical DVT. Another limitation is the small sample group diagnosed with subclinical DVT. A larger multicenter study would be required to recruit thousands of patients to have many subclinical DVT cases diagnosed. Finally, one of the limitations of our study was the lack of preoperative Doppler screening as it can be argued that patients developing postoperative subclinical DVT were already admitted to hospital with DVT. Further studies can investigate comparing preoperative and postoperative venous Doppler findings in high-risk patients.

These studies contribute to the literature on the importance of VTE prophylaxis in thoracic surgery. Our study needs to be supported by others on how centers can ensure the proper application of these guidelines on their patients as this is the major limiting risk factor for VTE and PE.

Conclusions

It can be concluded that the incidence of subclinical deep vein thrombosis is low in the postoperative period among patients undergoing lung resection for lung cancer if appropriate prophylactic measures are applied. However, patients with preoperative chemotherapy and those with longer periods of immobilization are at a higher risk of developing postoperative DVT despite anticoagulant prophylaxis. Due to the sample size and design limitations, the mentioned risk factors could be associated with DVT not a cause of DVT. It might be justified to screen these high-risk groups to detect subclinical DVT to allow for post-discharge prophylaxis.

Abbreviations

DVT	Deep venous thrombosis
VTE	Venous thromboembolism
LMWH	Low molecular weight heparin
VAS	Visual analogue score
VATS	Video-assisted thoracoscopic surgery
CSF	Cerebrospinal fluid
ICU	Intensive care unit
EBUS	Endobronchial ultrasound
EUS	Esophageal ultrasound

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Authors' contributions
HHE found the idea and formulated the methodology and revised the manuscript, AAE and AMM revised and supervised the manuscript, ME performed statistical analysis and revised the manuscript, and MMB wrote the manuscript and performed analysis.

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Declarations

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The authors declare that they have no competing interests.

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