

Preoperative Pneumonia and Postoperative Venous Thrombosis: A Cohort Study of 427,656 Patients Undergoing Major General Surgery

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Abstract

Background The literature is sparse regarding the association between pneumonia and venous thrombosis in surgical patients. The aim of this study was to investigate the risk of postoperative venous thrombosis in patients who fit the criteria for preoperative pneumonia using data from the ongoing American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database while adjusting for potential confounders.

Methods This is a cohort study using data from the ACS NSQIP database participating sites from 2008 (211 sites) and 2009 (237 sites). 427,656 patients undergoing major general surgery were included. The 30-day risk of postoperative venous thrombosis including deep vein thrombosis (DVT) and pulmonary embolism (PE) was evaluated in patients with preoperative pneumonia diagnosed before undergoing major general surgery.

Results Patients with preoperative pneumonia had a higher incidence of both 30-day DVT and PE than patients without preoperative pneumonia. After adjusting for all potential confounders, the effect estimates for the association between preoperative pneumonia and venous thrombosis were DVT, OR: 1.67 (95% CI 1.32–2.11) and PE, OR: 2.18 (95% CI 1.48–3.22).

Conclusions A large, multicenter database of surgical patients showed that preoperative pneumonia may increase risk for developing venous thrombosis. This adds to our understanding of risk factors for venous thrombosis and suggests a potential benefit of diagnosing preoperative pneumonia in patients undergoing major general surgery.

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Introduction

Venous thrombosis (VT), which primarily includes deep venous thrombosis (DVT) and pulmonary embolism (PE), continues to be a major cause of morbidity and mortality in postoperative patients. VT is a significant patient safety concern, and is considered to be an indicator of quality in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). The incidence of DVT in patients undergoing high risk general surgery is up to 25%, and that of PE is 1.6%, without the use of anticoagulants for thromboprophylaxis, incurring an increased hospitalization cost of over \$12,000 per patient [1, 2].

There have been recent population-based prospective studies as well as review articles of basic science and epidemiological studies, which show that elevated inflammatory markers such as C-reactive protein (CRP) as well as infectious processes are associated with an increased risk of VT [3–5].

The literature is sparse regarding the association between pneumonia and VT in surgical patients. A population-based study of the NSQIP cohort which only included patients from Veterans Health Administration Hospitals showed that patients who underwent surgery and developed postoperative pneumonia had an increased risk of VT with an odds ratio of 2.7 after adjusting for confounders. However, the authors did not find that ‘preoperative’ pneumonia was associated with an increased risk of VTE [6].

With this background, we sought to investigate the risk of postoperative VT in patients who fit the criteria for preoperative pneumonia using data from the ongoing ACS NSQIP database while adjusting for potential confounders.

Methods

This was a cohort study using data from the ACS NSQIP database. Details of the ACS NSQIP (www.acsnsqip.org) have been recently described [7] and are summarized in Supplement 1. It is a validated outcomes registry designed to provide feedback to member hospitals on 30-day risk-adjusted surgical mortality and morbidity [8, 9]. The database includes de-identified data on demographics, perioperative variables, and 30-day postoperative outcomes for adult patients undergoing major surgery in participating nonveteran’s administration hospitals [8]. Trained surgical clinical reviewers collect patient data upon admission from the medical chart, operative log, anesthesia record, interviews with the surgical attending, and telephone interviews with the patient [8]. Data quality is ensured through comprehensive training of the nurse reviewers, an inter-rater

reliability audit of participating sites, regular conference calls, and an annual meeting [10].

For this study, the available ACS NSQIP participant use files of the years 2008 (271,368 patients from 211 sites) and 2009 (336,190 patients from 237 sites) were retrieved for all major surgeries performed at participating ACS NSQIP medical centers. We included the subset of patients undergoing major general surgery in this study ($n = 427,656$). In accordance with the American University of Beirut’s guidelines (which follow the US Code of Federal Regulations for the Protection of Human Subjects), institutional review board approval was not needed or sought for our analysis because data were collected as part of a quality assurance activity.

Preoperative pneumonia

The ACS NSQIP database records data on all patients who have a new pneumonia or a recently diagnosed pneumonia on current antibiotic treatment at the time the patient is brought to the operating room. Patients must meet the below criteria for them to be registered as having preoperative pneumonia:

- (1) One definitive chest radiological exam [X-ray or computed tomography (CT)] with at least one of the following: new or progressive and persistent infiltrate; consolidation or opacity; or cavitation. In patients with underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), two or more serial chest radiological exams (X-ray or CT) are required.
- (2) At least one of the following: fever ($>38^{\circ}\text{C}$ or $>100.40^{\circ}\text{F}$) with no other recognized cause; leukopenia (<4000 white blood cells/ mm^3) or leukocytosis ($\geq 12,000$ white blood cells/ mm^3); or for adults ≥ 70 years old, altered mental status with no other recognized cause and
 - (A) At least one of the following: 5% bronchoalveolar lavage-obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram stain); positive growth in blood culture not related to another source of infection; positive growth in culture of pleural fluid; positive quantitative culture from minimally contaminated lower respiratory tract specimen (e.g., bronchoalveolar lavage or protected specimen brushing), or
 - (B) At least two of the following: new onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements; new onset or

worsening cough, or dyspnea, or tachypnea; rales or bronchial breath sounds; worsening gas exchange (e.g., O_2 desaturations (e.g., $PaO_2/FiO_2 \leq 240$), increased oxygen requirements, or increased ventilator demand).

Postoperative outcomes

Evaluated outcomes were 30-day postoperative venous thrombosis including DVT and PE, which were defined as follows:

- *DVT* the identification of a new blood clot or thrombus within the venous system, which may be coupled with inflammation. This diagnosis is confirmed by a duplex, venogram, or CT scan.
- *PE* lodging of a blood clot in a pulmonary artery with subsequent obstruction of blood supply to the lung parenchyma. The blood clots usually originate from the deep leg veins or the pelvic venous system. Diagnosis is documented if the patient has a ventilation/perfusion (V–Q) scan interpreted as high probability of PE or a positive CT spiral exam, pulmonary arteriogram, or CT angiogram.

Of note, ACS NSQIP records data from routine care. As such, there was no dedicated screening of patients. Diagnostic modalities were requested and performed as judged by clinical decision making.

Statistical analysis

Descriptive statistics are presented as means (standard deviation, SD), medians (interquartile range, IQR), and percentages. We calculated the unadjusted OR and 95% confidence intervals (CI) for several demographics and preoperative variables as risk factors for both preoperative pneumonia and 30-day venous thrombosis outcomes. We then evaluated the unadjusted and adjusted OR and 95% CI for 30-day venous thrombosis outcomes in patients with compared to those without preoperative pneumonia. Models were built using multivariate logistic regression analysis, by adjusting the association between preoperative pneumonia and outcomes for all variables listed in Table 1, which were considered potential confounders based on their association with pneumonia or venous thrombosis as determined in the medical literature or by clinical judgment. Adjustment for was done for each confounder individually and as a group.

Table 1 Patient's characteristics

Parameter	No pneumonia (<i>n</i> = 425,354)	Pneumonia (<i>n</i> = 2302)	OR for pneumonia (95% CI)
Age ≥ 65	28.0	49.5	2.52 (2.32–2.73)
Male	40.2	55.9	1.88 (1.74–2.05)
Race			
White	76.9	75.5	1.08 (0.95–1.23)
Black or African American	10.3	12.8	1.36 (1.15–1.61)
Other/unknown	12.8	11.7	Referent
Smoker during year prior	19.1	28.1	1.66 (1.51–1.82)
Chronic obstructive pulmonary disease	3.7	24.5	8.46 (7.68–9.31)
Ventilator dependence preoperatively	0.7	41.8	98.72 (90.21–108.03)
Congestive heart failure	0.6	14.4	30.19 (26.69–34.15)
Renal failure ^a	1.2	11.2	10.43 (9.14–11.91)
Obesity ^b	40.4	31.1	0.67 (0.61–0.73)
Diabetes ^c	13.5	24.2	2.01 (1.86–2.26)
Disseminated cancer	2.2	7.1	3.43 (2.92–4.02)
Chemotherapy in 30 days prior	1.2	4.2	3.58 (2.91–4.40)
Pregnancy	0.3	0.5	1.87 (1.06–3.30)
Prior operation within 30 days	2.4	27.9	15.58 (14.20–17.10)
Median duration from admission to operation in days	0.0	5.0	1.07 (1.07–1.08) ^d

Data presented as percentages, unless otherwise indicated

OR odds ratio, CI confidence interval

^a Currently on dialysis

^b Body mass index ≥ 30 kg/m²

^c On oral agents or insulin

^d Per each day increase

We also evaluated the association between preoperative pneumonia and potential intermediate factors (operative time and duration of postsurgical stay) along the causal pathway for postoperative venous thrombosis through linear regression analysis. The association between preoperative pneumonia and postoperative venous thrombosis was re-evaluated after adjustment for these factors.

Data were near complete with only missing values for body mass index ($n = 12,240$, 2.9%) which were imputed by the respective means of similar sex and age groups.

Results

Data from 427,656 patients were included in this study. Their mean age was 53.9 years (SD, 17.0 years) with 40.3% being men. The prevalence of preoperative pneumonia was 0.5% ($n = 2311$), while 99.5% of patients ($n = 425,354$) had no preoperative pneumonia. Patients with preoperative pneumonia were more commonly elderly, men, black, or African American, and current smokers than patients without preoperative pneumonia. They were also more likely to have chronic obstructive pulmonary disease, have preoperative ventilator dependence, congestive heart failure, renal failure, diabetes, or cancer; but less likely to be obese. There was also a higher proportion in pregnant women or patients who had a prior operation in the previous 30 days. They also had a higher median duration of preoperative hospital stay (Table 1).

Patients with preoperative pneumonia had a higher incidence of both 30-day DVT and PE than patients without preoperative pneumonia (Fig. 1). In unadjusted analysis, preoperative pneumonia had a strong and significant association with the occurrence of postoperative VT: DVT, OR: 8.20 (95% CI 6.75–9.96) and PE, OR: 5.07 (95% CI 3.63–7.07) (Table 2). Upon adjusting the association between preoperative pneumonia and postoperative VT for individual variables listed in Table 3, preoperative ventilator dependence, elderly age, chronic obstructive pulmonary disease, congestive heart failure, and prior operation within 30 days had the most apparent confounding. After adjusting for all potential confounders, the effect estimates for the association between preoperative pneumonia and VT were: DVT, OR: 1.67 (95% CI 1.32–2.11) and PE, OR: 2.18 (95% CI 1.48–3.22) (Table 3).

We also evaluated whether the observed effect of preoperative pneumonia on postoperative VT is mediated by increased operative time or duration of postsurgical hospital stay. There was a strong association between preoperative pneumonia and an increased duration of postsurgical hospital stay but not operative time (Table 4). Upon adjustment for operative time (as well as all factors described in Table 3), the effect estimates for the association between preoperative pneumonia and VT were essentially unchanged: DVT, OR: 1.72 (95% CI 1.35–2.18) and PE, OR: 2.27 (95% CI 1.53–3.36). However, upon adjustment for duration of postsurgical hospital stay (as

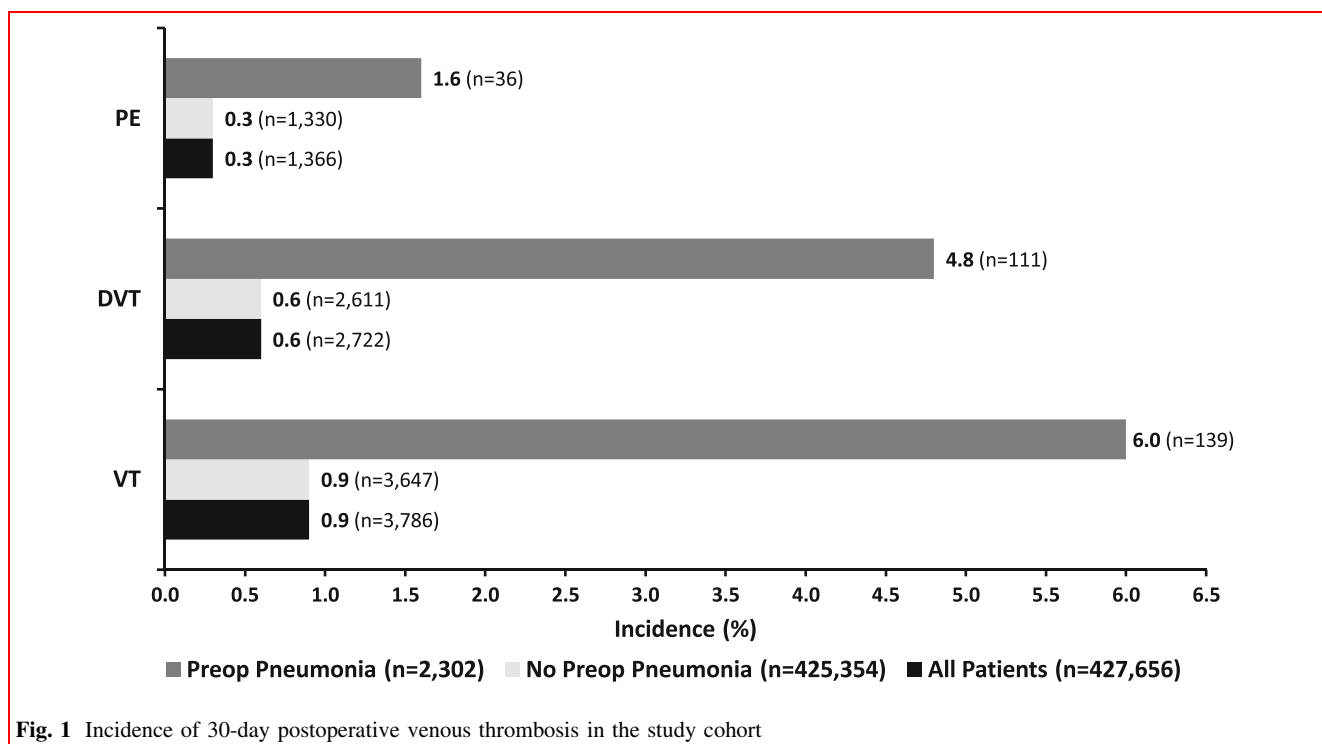


Fig. 1 Incidence of 30-day postoperative venous thrombosis in the study cohort

Table 2 Unadjusted odds ratios for 30-day postoperative venous thrombosis for evaluated risk factors

Risk factor	VT OR (95% CI)	DVT OR (95% CI)	PE OR (95% CI)
Preoperative pneumonia	7.43 (6.24–8.85)	8.20 (6.75–9.96)	5.07 (3.63–7.07)
Age \geq 65	2.65 (2.49–2.83)	2.75 (2.55–2.97)	2.46 (2.21–2.73)
Male	1.40 (1.32–1.50)	1.42 (1.32–1.54)	1.35 (1.21–1.50)
Race			
White	1.47 (1.32–1.65)	1.52 (1.33–1.74)	1.37 (1.14–1.64)
Black or African American	1.62 (1.41–1.87)	1.63 (1.37–1.92)	1.55 (1.23–1.95)
Other/unknown	Referent	Referent	Referent
Smoker during year prior	0.93 (0.85–1.01)	0.93 (0.85–1.03)	0.81 (0.70–0.94)
Chronic obstructive pulmonary disease	2.85 (2.56–3.18)	2.87 (2.53–3.26)	2.56 (2.13–3.08)
Ventilator dependence preoperatively	7.82 (6.85–8.92)	9.61 (8.34–11.08)	3.52 (2.61–4.77)
Congestive heart failure	4.85 (3.99–5.89)	5.44 (4.38–6.75)	2.97 (2.00–4.42)
Renal failure	2.36 (1.94–2.86)	2.94 (2.39–3.61)	1.12 (0.71–1.76)
Obesity	0.93 (0.87–0.99)	0.87 (0.80–0.94)	1.15 (1.03–1.27)
Diabetes	1.46 (1.35–1.59)	1.51 (1.37–1.66)	1.29 (1.12–1.49)
Disseminated cancer	3.26 (2.87–3.71)	3.24 (2.79–3.77)	3.06 (2.46–3.80)
Chemotherapy in 30 days prior	3.10 (2.61–3.69)	3.24 (2.65–3.95)	2.78 (2.06–3.75)
Pregnancy	0.75 (0.37–1.50)	0.65 (0.27–1.57)	1.04 (0.39–2.78)
Prior operation within 30 days	4.04 (3.62–4.52)	4.63 (4.09–5.23)	2.50 (2.00–3.12)
Duration from admission to operation in days	1.03 (1.03–1.03) ^a	1.03 (1.03–1.03) ^a	1.02 (1.01–1.02) ^a

VT venous thrombosis (DVT or PE), DVT deep vein thrombosis, PE pulmonary embolism, OR odds ratio, CI confidence interval

^a Per each day increase

Table 3 Adjusted odds ratios for 30-day postoperative venous thrombosis in patients with preoperative pneumonia compared with patients without after adjustment for potential confounders

Adjustment	Preoperative pneumonia OR (95%) for		
	VT	DVT	PE
Unadjusted	7.43 (6.24–8.85)	8.20 (6.75–9.96)	5.07 (3.63–7.07)
Adjusted for			
Age \geq 65	6.07 (5.09–7.24)	6.65 (5.46–8.09)	4.17 (2.98–5.83)
Male	7.08 (5.94–8.43)	7.80 (6.42–9.47)	4.84 (3.47–6.77)
Race	7.39 (6.21–8.80)	8.16 (6.72–9.92)	5.03 (3.61–7.03)
Smoker during year prior	7.50 (6.29–8.93)	8.27 (6.81–10.05)	5.16 (3.70–7.21)
Chronic obstructive pulmonary disease	5.79 (4.84–6.93)	6.40 (5.24–7.81)	4.01 (2.85–5.63)
Ventilator dependence preoperatively	2.70 (2.18–3.34)	2.46 (1.94–3.12)	3.33 (2.24–4.96)
Congestive heart failure	5.81 (4.82–7.00)	6.24 (5.06–7.69)	4.39 (3.09–6.22)
Renal failure	6.84 (5.72–8.17)	7.28 (5.97–8.88)	5.09 (3.63–7.12)
Obesity	7.39 (6.21–8.80)	8.11 (6.67–9.85)	5.13 (3.68–7.17)
Diabetes	7.13 (6.00–8.50)	7.85 (6.46–9.53)	4.93 (3.53–6.88)
Disseminated cancer	6.84 (5.74–8.16)	7.55 (6.21–9.18)	4.65 (3.33–6.50)
Chemotherapy in 30 days prior	7.09 (5.95–8.45)	7.80 (6.41–9.48)	4.84 (3.46–6.76)
Pregnancy	7.44 (6.25–8.85)	8.21 (6.76–9.97)	5.07 (3.63–7.07)
Prior operation within 30 days	4.82 (4.01–5.79)	4.99 (4.06–6.13)	3.94 (2.79–5.57)
Duration from admission to operation in days	5.72 (4.77–6.85)	6.33 (5.18–7.75)	4.26 (3.03–5.97)
All risk factors	1.79 (1.45–2.21)	1.67 (1.32–2.11)	2.18 (1.48–3.22)

VT venous thrombosis (DVT or PE), DVT deep vein thrombosis, PE pulmonary embolism, OR odds ratio, CI confidence interval

Table 4 Association between preoperative pneumonia and operative time or duration of postsurgical hospital stay

Parameter	Operative time (min)	Duration of postsurgical hospital stay (days)
Median (IQR)		
No preoperative pneumonia	77 (46–131)	1 (0–4)
Preoperative pneumonia	87 (53–133)	12 (6–24)
Unadjusted linear regression analysis ^a		
Constant (95% CI)	102.55 (102.29–102.80)	3.47 (3.45–3.49)
Beta (95% CI)	1.79 (–1.74 to 5.31)	14.96 (14.67–15.25)
Adjusted linear regression analysis ^{a,b}		
Constant	88.60 (87.85–89.53)	2.16 (2.10–2.22)
Beta (95% CI)	–6.43 (–10.13 to –2.72)	4.14 (3.86–4.43)

IQR interquartile range, CI confidence interval

^a For preoperative pneumonia vs. no preoperative pneumonia

^b Adjusted for all variables described in Table 3

well as all factors described in Table 3), the effect of preoperative pneumonia on the risk of VT seemed to be partly explained by increased duration of postsurgical hospital stay. The effect estimates for preoperative pneumonia became: DVT, OR: 1.52 (95% CI 1.19–1.94) and PE, OR: 1.84 (95% CI 1.24–2.71).

Discussion

The current analysis of a large, multicenter database of surgical patients showed that preoperative pneumonia may increase the risk for developing VT, even after adjusting for all possible confounders. This risk was still elevated, though attenuated, after adjusting for postsurgical hospital stay. Interestingly, we did not find that increased operative time added to the risk of VT in patients with preoperative pneumonia. A previous prospective observational study showed that an operative time of more than two hours conferred a 4.5-fold increased risk of VT; however, they did not analyze patients with preoperative infections or pneumonia [11]. This study is the first to show a potential association between preoperative pneumonia and postoperative VT. The findings are contrary to a previous study which failed to show such an association [6], although it was primarily conducted in elderly male veterans.

The association and possible causality between pneumonia and VT in nonsurgical patients has been demonstrated in two separate studies of large-scale primary care databases, with a peak incidence between 2 and 4 weeks of being diagnosed with a respiratory infection, with still apparent, albeit decreased risk, up to one year later [12, 13]. After adjusting for confounders, one study found an OR of 2.6 for VT and the other found an incidence rate ratio of 4.9 for in-hospital patients versus 3.4 for community-treated patients. In both studies, the risk of VT was the

highest in respiratory tract infections as compared to other types of infections. These data correspond to the results of the current study whereby in the unadjusted analysis preoperative pneumonia one of the highest effects on the occurrence of postoperative VT among risk factors that were evaluated. These results are also in agreement with our findings in postoperative surgical patients whereby there was an increased risk of developing a postoperative DVT (OR 1.67) and PE (OR 2.18) when there was evidence of preoperative pneumonia, even after correcting for all possible confounders.

The increased risk was attenuated after correcting for the length of hospital stay, down to an OR of 1.52 and 1.84 for DVT and PE, respectively, pointing toward the likelihood of immobility as a possible mechanism for the development of VT. Alternatively, it may also be because the causal pathway was adjusted, with pneumonia leading to a longer hospital stay. A recent, large, population-based, case–control study showed a 3.8-fold increased risk of VT in patients diagnosed with pneumonia after correcting for confounders, including unhealthy lifestyle factors and immobilization [14]. The authors pointed out that the lack of other known confounders to explain this increased risk pointed to the possible causality of pneumonia itself in conferring an increased risk of VT.

A recent population-based prospective study showed that elevated CRP was associated with an increased risk of VT, confirming the findings of a review article in 2005 that showed an association between inflammatory markers and VT, with OR from two to six [3, 4]. A recent NSQIP review found that postoperative patients with inflammatory bowel disease had a greater risk of VT than patients with colorectal cancer [15]. Additionally, a recent review paper, which included basic science and epidemiological studies that evaluated infection and inflammation as risk factors for VT, concluded that a strong association between acute active

inflammation as well as infectious processes and the occurrence of VT, with an overall 2–4-fold increased risk for VT being highlighted [5]. In one of the studies analyzed, the risk was the highest with a two-fold OR during the first 2 weeks following the diagnosis of pneumonia, and this risk dissipated to reach reference levels within 26 weeks [16]. These data were subsequently reproduced by several large, population-based studies [17]. These associations correspond to the results of the current study. The increased inflammatory response in patients with preoperative pneumonia may partially explain the increased risk of VT in these patients. Unfortunately, we do not have data on inflammatory markers to confirm such a hypothesis.

One potential limitation of this study was that we were unable to control for hospital effects owing to the absence of hospital identifiers in our data. There may have been variability in-hospital quality or variability in surgical strategy which may have potentially confounded the association between risk factors and outcome. We reported adverse outcome rates applicable in a population with a similar case mix as that generated by the ACS NSQIP sampling strategy. If our findings are to be extrapolated to settings with higher adverse outcome rates, such relative increases would be of more apparent clinical significance. The ACS NSQIP database does not record prior history of VT or use of anticoagulant therapy. Had these measures been present more commonly in patients with preoperative pneumonia or associated risk factors, the estimates of postoperative VT may have been over- or underestimated, respectively. Although adjustment for the association between preoperative pneumonia and VT was made for the potential confounding effects of several known risk factors, omitted variables and residual confounding remain characteristic of observational studies; thus, the effects of additional confounding factors like other co-existing infections or inflammatory disorders that can have an association with preoperative pneumonia or VT outcomes cannot be fully excluded.

This study adds to our understanding of the possible risk factors for VT in the surgical patients, and suggests a potential benefit from early diagnosis and management of preoperative pneumonia especially in elective surgery patients.

Compliance with ethical standards

Conflict of interest None.

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