



# Antiplatelet Drugs and Risk of Bleeding After Bedside Pleural Procedures

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**Title:** Antiplatelet drugs and risk of bleeding after bedside pleural procedures: a national multicenter cohort study

**Short title:** Antiplatelet drugs and bleeding after pleural procedures

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10

1   **Abstract**

2   **Background.** The decision making on antiplatelet drug withdrawal or continuation before performing a  
3   pleural procedure is based on the balance between the risk of bleeding associated with the antiplatelet  
4   therapy and the risk of arterial thrombosis due to its interruption. Knowledge on antiplatelet therapy-  
5   associated risk of bleeding after pleural procedure is lacking.

6   **Research Question.** Is the risk of bleeding associated with antiplatelet drugs increased in patients  
7   undergoing pleural procedures?

8   **Study Design and Methods.** We conducted a French multicenter cohort study in 19 centers. The main  
9   outcome was the occurrence of bleeding, defined as hematoma, hemoptysis or hemothorax, during the 24  
10   hours following the pleural procedure. Serious bleedings were defined as bleeding requiring blood  
11   transfusion, respiratory support, endotracheal intubation, embolization, surgery or death.

12   **Results.** A total of 1124 patients was included (66% of men, median age of  $62.6 \pm 27.7$  years), of whom 182  
13   were on antiplatelet therapy and 942 were not. Fifteen patients experienced a bleeding event including  
14   eight serious bleedings. The 24-hour incidence of bleeding was 3.23% (95% CI, 1.08 to 5.91) in the  
15   antiplatelet group and 0.96% (95% CI, 0.43 to 1.60) in the control group. The occurrence of bleeding events  
16   was significantly associated with antiplatelet therapy in univariate (OR, 3.44; 95% CI, 1.14 to 9.66;  $p=0.021$ )  
17   and multivariate analysis (OR, 4.13; 95% CI, 1.01 to 17.03;  $p=0.044$ ) after adjusting for demographic data  
18   and the main risks factors for bleeding. Likewise, antiplatelet therapy was significantly associated with  
19   serious bleeding in univariate (OR, 8.61; 95% CI, 2.09 to 42.3;  $p=0.003$ ) and multivariate analysis (OR, 7.27;  
20   95% CI, 1.18 to 56.1;  $p=0.032$ ) after adjusting for the number of risk factors for bleeding.

21   **Interpretation.** Antiplatelet therapy was associated with an increased risk of post-pleural procedure  
22   bleeding and serious bleeding. Future guidelines should take into account these results for patient safety.

23

24   **Key words:** antiplatelet drug; bleeding risk; pleural procedure; thoracentesis; chest tube insertion; closed  
25   pleural biopsy.

## 1    **Introduction**

2    Pleural disorders affect over 3000 people per million population each year in developed countries (1),  
3    caused by a wide range of pathologies, in particular congestive heart failure, infection, and cancer. Pleural  
4    procedures (thoracentesis, closed pleural biopsy, or chest tube insertion) are key to diagnosis (2) and may  
5    also be the main therapeutic approach in conditions such as pneumothorax (3). All of these procedures  
6    entail a risk of bleeding, which is infrequent but may be life-threatening (4). Patients taking concomitant  
7    antiplatelet drugs would usually be considered at higher risk for this complication, raising the question  
8    antiplatelet therapy discontinuation before pleural procedures. However, withdrawing antiplatelet drugs  
9    may have adverse consequences in patients with coronary (5) or cerebral (6) vascular diseases at high risk  
10   of thrombosis. Long-term antiplatelet therapy is now commonly prescribed and the risk of thrombosis after  
11   their withdrawal well known. In contrast, data on the risk of post-pleural procedure bleeding associated  
12   with antiplatelet therapy are scant. Previous studies have reported low rates of hemorrhagic complications  
13   after pleural procedures in patients receiving antiplatelet therapy. However, they were single-center  
14   studies and included few patients (7)(8)(9), in particular the size of study populations was below the  
15   number of procedures necessary to observe even one bleeding event after pleural procedures. In other  
16   areas, the increased risk of bleeding in patients receiving antiplatelet drugs after chest surgery,  
17   bronchoscopy, or interventional pulmonary procedures is well established and has led to guidelines on the  
18   management of antiplatelet drugs before procedures (10)(11)(12). In contrast, the current international  
19   guidelines for pleural procedures do not address the question of antiplatelet drug management (2)(13). The  
20   general guidance on all percutaneous procedures in patients taking antiplatelet drugs noted that its  
21   recommendations for pleural procedures were limited due to the weakness of available data (14). In  
22   consequence, clinical decision making is heterogeneous (15) and patient safety potentially compromised.  
23   The current study was conceived to assess the risk of bleeding and serious bleeding associated with  
24   antiplatelet drugs in patients undergoing pleural procedures.

## 1    **Methods**

### 2    **Setting and patients**

3    We conducted a multicenter cohort study involving 19 French centers (eight respiratory care departments  
4    and 11 intensive care units in 14 university teaching hospitals and five general hospitals). All patients  
5    undergoing bedside thoracentesis, closed pleural biopsy or chest tube insertion from November 2011 to  
6    January 2014 were considered for inclusion. We excluded patients aged less than 18, those with  
7    hemothorax, recent chest surgery, receiving full anticoagulation or under extracorporeal membrane  
8    oxygenation. Participants were considered to be in the exposed (or antiplatelet) group if they were  
9    receiving antiplatelet drugs at the time of the procedure and at least five days before the procedure. They  
10    were considered to be in the unexposed (or control) group if they had never been under antiplatelet  
11    therapy or were free from antiplatelet drugs during at least five days before the pleural procedure (16) (17)  
12    (18) (19). To avoid confusion regarding the evaluation of bleeding risk, patients in whom antiplatelet drugs  
13    had been interrupted for any reason during the five days preceding the pleural procedure were not  
14    included in the study.

15    The study was approved by the Institutional Review Board of the French Language Respiratory Society  
16    (Société de Pneumologie de Langue Française, CEPRO 2011-051) and was declared to the National  
17    Commission on Informatics and Liberty (CNIL 911367). Study information was included in an information  
18    booklet routinely given to all patients prior to thoracentesis, closed pleural biopsy or chest tube insertion  
19    during the study period. French legislation on noninterventional studies requires collecting non-opposition  
20    of patients but does not require written consent. As such, non-opposition was obtained from each patient  
21    included in the study for the use of their deidentified medical records data. Participants did not receive  
22    financial compensation.

### 23    **Outcomes**

24    The main outcome was the occurrence of "bleeding", defined as the occurrence of hematoma, hemoptysis  
25    or hemothorax, during the 24 hours following the pleural procedure. The secondary outcome was the  
26    occurrence of "serious bleeding" during the 24 hours post pleural procedure, defined as bleeding requiring  
27    blood transfusion, respiratory support, endotracheal intubation, embolization or surgery, or when death  
28    occurred. In the event of bleeding, the interventions required (follow-up, blood transfusion, respiratory  
29    support, endotracheal intubation, embolization or surgery) were recorded, as was the occurrence of death.

### 30    **Other measurements and risk factor for bleeding**

31    We documented demographic (age, gender, body mass index) and biological data (platelets count,  
32    prothrombin time (PT), activated partial thromboplastin time (APTT) ratio, creatinine clearance, measured  
33    the day or the day before the procedure), as well as procedure characteristics (operator experience,  
34    diameter of pleural device, and radiographic guidance). Radiographic guidance included both  
35    ultrasonographic and Computed Tomography (CT) scan guidance, the latter one consisting in marking the  
36    puncture site using a felt tip pen during a chest CT scan; then, pleural procedure was performed at bedside

without real-time guidance. We determined risk factors for bleeding for each patient. Intrinsic risk factors for bleeding were defined as age > 65 years, platelet count < 100  $10^9/L$ , PT < 50%, APTT > 1.4, and moderate and severe renal failure (creatinine clearance < 60 and 30  $L \cdot min^{-1}$  as assessed with Cockcroft-Gault formula (2)(12)(13)). Extrinsic risk factors for bleeding were defined as junior operator (resident or medical student), experience of operator < 50 procedures, no image-guidance for pleural procedure, and pleural device diameter > 14F.

## **Statistical analysis**

Study group characteristics were described using mean  $\pm$  standard deviation, or median  $\pm$  interquartile range in case of non-normality, for quantitative variables and number (percentage) for qualitative variables. Comparison between groups was performed using Student's *t*-test, or Wilcoxon tests in case of non-normality, for quantitative variables and Fisher exact tests for qualitative variables. The 24-hour incidence of bleeding (and serious bleeding) was calculated in the whole population, in the exposed to antiplatelet therapies group and in the control group. Because the number of events was low, the 95% confidence intervals (CI) were computed using a bias-corrected accelerated bootstrap method with 10,000 replications (20).

To assess the association between bleeding events, as the dependent variable, and antiplatelet drugs as the explanatory variable, we first conducted univariate analyses using univariate logistic regression. The main logistic multivariate model was constructed considering baseline characteristics for adjustment: (i) excluding the collinear covariates (highly associated each other, e.g. pleural procedure and pleural device diameter); (ii) choosing the covariates most associated with the dependent variable in univariate analysis when the quantitative or qualitative covariate was available (e.g. PT); and (iii) assessing the linearity between the dependent variable and quantitative covariates using cubic splines in adjusted generalized additive models. The main model was then adjusted for gender, age, platelet count, PT, APTT ratio, moderate renal failure, department, pleural procedure, operator experience and radiographic guidance. Because the number of events was small relative to the number of covariates, we have taken care to verify the convergence of the model (control of the number of iterations, stability of the coefficients and standard errors during the successive addition of the covariates). Interaction terms between antiplatelet drugs and the covariates were tested one at a time in multivariate logistic models. In addition, we conducted sensitivity analyses: (i) using a backward stepwise selection; and (ii) using the Firth's bias-Reduced penalized-likelihood logistic regression adapted to rare events (21), adjusted for the same covariates that within the main model. Finally, to assess the center effect, we added the center as a random-effect in a univariate generalized linear mixed-effects model; adjustments were not possible because of problems of convergence of the model. Results were expressed as odds ratios (OR) with 95% confidence interval (CI). Given the rarity of the events, the association between serious bleeding events and antiplatelet drugs was study using a univariate logistic regression, and a multivariate analysis only adjusted for the number of total (intrinsic and extrinsic) bleeding risk factors per patient.



- 1 All statistical analyses were performed using R software, version 3.5.2 (22). The threshold for statistical
- 2 significance was 0.05.

## 1 Results

### 2 Patients and procedures

3 The study population consisted of 1124 patients, 737 (66%) men and 387 (34%) women, whose median age  
4 was  $62.6 \pm 27.7$  years. Among them, 182 were taking antiplatelet drugs (142 treated by aspirin, 17 by  
5 clopidogrel, 22 by aspirin and clopidogrel, and one by aspirin and prasugrel), and 942 were not. Pleural  
6 procedures consisted of 377 thoracenteses, 130 closed pleural biopsies and 617 chest tube insertions  
7 (including 343 surgical and 270 percutaneous chest tube insertions; four missing values). The procedure  
8 was indicated for pleural effusion in 80% and pneumothorax in 20% of the whole population (**Table 1**).  
9 Patients taking antiplatelet drugs were more likely to be men (73% vs 64%,  $p=0.028$ ) and older (76% vs 39%  
10 over 65 years,  $p<0.001$ ), and to have a higher body mass index ( $24.4 \pm 6.5$  vs  $22.7 \pm 5.7$   $\text{kg.m}^{-2}$ ,  $p<0.001$ ) and  
11 a poorer renal function (50% vs 27% for moderate renal failure,  $p<0.001$ ). They were less likely to have  
12 thrombopenia (2% vs 8%,  $p=0.004$ ). Differences in PT and APTT ratio between groups did not reach  
13 significance. The indication for pleural effusion was higher in the antiplatelet group (89% vs 78%,  $p<0.001$ ).  
14 In the antiplatelet group, the rate of image-guidance was higher (77% vs 68%,  $p=0.01$ ). The rate of image  
15 guidance was significantly higher when pleural procedure was performed for pleural effusion than for  
16 pneumothorax (82% vs 21%,  $p<0.001$ ). Among the 781 patients having radiologic guidance, 689 were  
17 ultrasonographic guidance and 92 were CT scan guidance. We did not observe significant difference  
18 between groups for operator experience and pleural device diameter (**Table 1**). The kind of pleural  
19 procedure was highly associated with the indication ( $p<10^{-9}$ ) and the pleural device diameter ( $p<10^{-9}$ ).  
20 Likewise, the experience of the operator was highly associated with the senior or junior doctor status  
21 ( $p<10^{-9}$ ).

### 22 Description of bleeding events

23 Fifteen bleeding events occurred, six in the antiplatelet group and nine in the control group, including nine  
24 hemothorax, two hemoptysis, and three hematomas. In one case, the nature of the bleeding event was not  
25 documented in the electronic form. Nine events occurred after chest tube insertion (two after surgical and  
26 six after percutaneous chest tube insertions ( $p=0.15$ ); one missing value), five after thoracentesis and one  
27 after closed pleural biopsy. It means that 1.5% of chest tube insertions, 1.3% of thoracenteses and 0.8% of  
28 closed pleural biopsies led to bleeding ( $p>0.99$ ). The 24-hour incidence of bleeding was 1.33% (95% CI, 0.71  
29 to 2.05) in the whole population, 3.23% (95% CI, 1.08 to 5.91) in the antiplatelet group and 0.96% (95% CI,  
30 0.43 to 1.60) in the control group. In the antiplatelet group, all bleeding events occurred in patients taking  
31 aspirin monotherapy.

32 Eight serious bleeding events occurred, five in the antiplatelet group and three in the control group.  
33 Overall, 83.3% of bleeding events occurring in patients on antiplatelet therapy were serious vs 33.3% in  
34 controls. No death occurred. Five serious bleeding events occurred after chest tube insertion, two after  
35 thoracentesis, and one after closed pleural biopsy. In other terms, 0.8% of chest tube insertions, 0.5% of  
36 thoracenteses and 0.8% of closed pleural biopsies led to serious bleeding ( $p = 0.89$ ). The 24-hour incidence

1 of serious bleeding was 0.71% (95% CI, 0.27 to 1.25) in the overall study group, 2.69% (95% CI, 0.54 to 5.38)  
2 in the antiplatelet group and 0.32% (95% CI, 0 to 0.75) in the control group.

3 **Association between bleeding events and antiplatelet therapy**

4 In univariate analysis, the occurrence of bleeding events was significantly associated with antiplatelet  
5 therapy (OR, 3.44; 95% CI, 1.14 to 9.66; p=0.021). It was also significantly associated with platelet count  
6 (OR, 0.44; 95% CI, 0.25 to 0.73 per 100 G.L-1 increase; p=0.002), PT level (OR, 0.76; 95% CI, 0.61 to 0.97 per  
7 10% increase; p=0.020), APTT ratio (OR, 3.18; 95% CI, 1.26 to 6.81 per one unit increase; p=0.006),  
8 increased APTT ratio > 1.4 (OR, 3.28; 95% CI, 1.01 to 9.39; p=0.033), and severe renal failure (OR, 4.68; 95%  
9 CI, 1.01 to 16.60; p=0.025) (**Table 2**). In multivariate analysis, after adjusting for gender, age, platelet count,  
10 PT, APTT ratio, moderate renal failure, department, pleural procedure, operator experience and  
11 radiographic guidance, the occurrence of bleeding events was significantly associated with antiplatelet  
12 therapy (OR, 4.13; 95% CI, 1.01 to 17.03; p=0.044) (**Table 2**). The analysis showed no significant interaction  
13 of any covariable with antiplatelet therapy (data not shown). In sensitivity analyses, we also observed an  
14 association between the occurrence of bleeding events and antiplatelet therapy using (i) the stepwise  
15 procedure (OR, 5.16; 95% CI, 1.41 to 18.36; p=0.010) (**Table 2**); and (ii) the Firth's bias-Reduced penalized-  
16 likelihood logistic regression (OR, 4.02; 95% CI, 2.62 to 8.44). Finally, the univariate association between the  
17 occurrence of bleeding and antiplatelet therapy was similar and remained significant when adding the  
18 center as a random-effect (OR, 3.40; 95% CI, 1.11 to 9.72; p=0.024).

19 Likewise, antiplatelet therapy was significantly associated with the risk of serious bleeding (OR, 8.61; 95%  
20 CI, 2.09 to 42.3; p=0.003) in univariate analysis. This association remained statistically significant after  
21 adjustment for the number of bleeding risk factors per patient (OR, 7.27; 95% CI, 1.18 to 56.1; p=0.032).

## Discussion

In our study, antiplatelet therapy was identified as an independent risk factor for post-pleural procedure bleeding (OR, 4.13; 95% CI, 1.01 to 17.03; after adjustment for the main risk factors of bleeding) and serious bleeding (OR, 7.27; 95% CI, 1.18 to 56.1;  $p=0.032$ ; after adjustment for the number of risk factors of bleeding). These findings are the first to firmly demonstrate the relationship between antiplatelet therapy and post-pleural procedures bleeding events and to give an estimation of the rate of bleedings in patients taking antiplatelet therapy at the time of the procedure. They are consistent with a previous study, which reported one case of severe hemothorax after thoracentesis among twenty-five patients treated with clopidogrel while none of the fifty controls experienced bleeding (9). In contrast, two other studies, limited by small study sample and design, did not find any significant bleeding after pleural procedure in patients taking antiplatelet therapy (7)(8).

Overall, antiplatelet therapy is associated with an increased risk of bleeding and blood product usage after all kinds of surgery (10). In the pulmonary interventional field, *Ernst and al.* reported in a prospective cohort study of 604 patients undergoing transbronchial lung biopsy, including 30 patients on clopidogrel, that the rate of bleeding was dramatically increased in patients taking clopidogrel (88% vs 3.4% in controls, including 34% of moderate and 27% of major bleeding) (23). In contrast, in a large retrospective analysis of 15,181 percutaneous core biopsies, including 1,174 lung biopsies, *Atwell and al.* reported a similar rate of bleeding in patients taking aspirin (0.6%,  $n=3,195$ ) and controls (0.4%,  $n=11,986$ ;  $p=0.34$ ) (24). However, this later study was highly limited by the definition of aspirin use based on the ingestion of aspirin within the 10 days preceding the biopsy but not specifically at the time of the procedure.

The risk of bleeding following a percutaneous procedure is arbitrarily classified as high when the rate of bleeding is over 1.5% in the general population or when they are performed in vital organs (14). In our study, we found a low rate of bleeding after pleural procedure in the overall study population, evaluated at 1.33% (95% CI, 0.71 to 2.05). Previous studies have reported variable rates of post-pleural procedures bleeding ranging from 0 to 3.8% for thoracentesis (25)(26)(27)(28), 0 to 12.5% for closed pleural biopsy (2)(29)(30)(31), and 0 and 4.2% for chest tube insertion (32)(33)(34). These studies were not designed to specifically address the question of hemorrhagic complications related to pleural procedures and they predate the publication of guidelines for pleural procedures (2)(13). A more recent audit conducted in the United Kingdom found results similar to ours with 1.1% of hemothorax and 1% of chest wall hematomas among 1162 thoracenteses, and 1.3% iatrogenic hemothorax among 1394 chest tube insertions (4). In this study, the impact of antiplatelet therapy on bleeding events was not analyzed. Although hemorrhagic complications of pleural procedures were infrequent in the UK study and ours, they can be life-threatening. In our study, we found a rate of severe bleeding at 0.71% (95% CI, 0.27 to 1.25) in the overall population. Fortunately, there were no deaths among our patients, however post-pleural hemorrhagic complications are known to be possibly fatal (4). The rate of bleeding might have been lower if all the patients had received radiological guidance, as recommended (4). Indeed, we observed that only 69% of the procedures

were realized under radiologic guidance. However, at the beginning of the study, the BTS guidelines were relatively recent and we hypothesize that practices in the centers involved in this study had not been modified yet. One patient with severe bleeding in the antiplatelet group had no radiologic guidance.

Altogether, these data suggest that antiplatelet therapy should be systematically stepped down to the minimum acceptable relative to the patient's thrombotic risk before any pleural procedure is undertaken. These results are of particular importance since they represent a change to current practice in pulmonology (15).

Our study was not designed to evaluate the risk of thrombosis in patients who had stopped antiplatelet therapy for the procedure. However, we know from previous studies that, in patients at high risk of thrombosis, discontinuation of antiplatelet therapy is an independent predictor of death, transient ischemic attack, and acute coronary syndromes (35)(36)(37)(38)(39). In our study, we found a frequency of bleeding at 3.23% (95% CI, 1.08 to 5.91) and of severe bleeding at 2.69% (95% CI, 0.54 to 5.38) in patients undergoing pleural procedures while receiving antiplatelet therapy; and none led to death. This risk may be considered as acceptable when balanced with the risk of a serious cardiovascular event associated with antiplatelet drug withdrawal in patients at high risk of thrombosis. If pleural procedures must be performed under antiplatelet therapy, a personalized approach should be performed including a comprehensive bleeding risk assessment, correction of all additional risk factors for bleeding and a particular attention to all aspects of the technique.

The main limit of the study is the presence of missing data, especially concerning renal function. In addition, the low number of events limited the multivariate analysis. However, we could construct a converging multiple linear model adjusted for the main risk factors of bleeding. Furthermore, this low number of events resulted in low statistical power that possibly explained that usual risk factors for bleeding were not associated with bleeding in the multivariate model. In addition, our study was not design to evaluate the risk of bleeding according to the antiplatelet agent. All bleedings occurred in patients treated by aspirin in monotherapy. No extra precautions were taken in patients receiving dual antiplatelet therapy, the absence of bleeding was probably due to the small number of patients in this group. Doses of aspirin were not recorded but supposed to be low (between 75 mg to 160mg per day) according to the French guidelines that recommend low doses of aspirin in cardiovascular diseases. Finally, our study pertains to bedside procedures only; the corresponding observations and interpretation cannot be extrapolated to CT-guided or surgical procedures.

## **Conclusion**

Antiplatelet therapy was associated with an increased risk of post-pleural procedure bleeding and serious bleeding that should be taken into account in the benefice/risk balance when considering a pleural

1 procedure in a patient taking antiplatelet drugs. However, the rates of bleeding and severe bleeding were  
2 low, advocating that pleural procedures may be performed with an acceptable risk when antiplatelet  
3 therapy cannot be interrupted.

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5   Jonathan Giovannelli performed the statistical analysis, contributed to the analysis and interpretation of  
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7   Gilles Mangiapan contributed to the acquisition and interpretation of data, revised the work critically for  
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**Table 1: Description of patients and pleural procedures.**

Characteristics	N	All patients (n = 1124)	Antiplatelet group (n = 186)	Control group (n = 938)	p value
Male gender — no. (%)	1124	737 (66%)	135 (73%)	602 (64%)	0.028
Age (year) — median ± IQR	1115	62.6 ± 27.7	75.8 ± 17.1	60.1 ± 28.4	< 0.001
Age > 65 years — no. (%)	1115	499 (45%)	139 (76%)	360 (39%)	< 0.001
BMI (kg.m <sup>-2</sup> ) — median ± IQR	868	23.0 ± 5.7	24.4 ± 6.5	22.7 ± 5.7	< 0.001
Platelets count (G.L <sup>-1</sup> ) — median ± IQR	1111	261 ± 156	263 ± 150	260 ± 158	0.35
Platelets < 100 G.L <sup>-1</sup> — no. (%)	1111	75 (7%)	4 (2%)	71 (8%)	0.004
PT (%) — median ± IQR	1048	83 ± 23	79 ± 24	83 ± 22	0.05
PT < 50% — no. (%)	1048	61 (6%)	7 (4%)	54 (6%)	0.37
APTT ratio — median ± IQR	975	1.03 ± 0.30	1.06 ± 0.32	1.03 ± 0.28	0.08
APTT > 1.4 — no. (%)	975	132 (14%)	25 (15%)	107 (13%)	0.62
Creatinine Cl. (L.min <sup>-1</sup> ) — median ± IQR	955	82.0 ± 61.5	60.3 ± 47.4	87.1 ± 61.3	< 0.001
Creatinine Cl. < 60 L.min <sup>-1</sup> — no. (%)	955	296 (31%)	77 (50%)	219 (27%)	< 0.001
Creatinine Cl. < 30 L.min <sup>-1</sup> — no. (%)	955	73 (8%)	24 (15%)	49 (6%)	< 0.001
Indication for pleural procedure — no. (%)	1124				< 0.001
Pleural effusion		899 (80%)	166 (89%)	733 (78%)	
Pneumothorax		225 (20%)	20 (11%)	205 (22%)	
Pleural procedure — no. (%)	1124				0.14
Chest tube insertion		617 (55%)	94 (50%)	523 (56%)	
Thoracentesis		377 (33%)	74 (40%)	303 (32%)	
Closed pleural biopsy		130 (12%)	18 (10%)	112 (12%)	
Type of department — no. (%)	1124				0.52
Respiratory Medicine		614 (55%)	106 (57%)	508 (54%)	
Intensive Care Medicine		510 (45%)	80 (43%)	430 (46%)	
Senior operator — no. (%)	1124	524 (47%)	86 (46%)	438 (47%)	0.89
Experience of operator < 50 procedures — no. (%)	1124	596 (53%)	95 (51%)	501 (53%)	0.62
Image-guidance — no. (%)	1124	781 (69%)	144 (77%)	637 (68%)	0.011
Pleural device diameter > 14F — no. (%)	1063	329 (31%)	45 (26%)	284 (32%)	0.15

IQR: interquartile range; BMI: Body Mass Index; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; APTT ratio: patient/control APTT ratio; Cl: clearance.

**Table 2: Associations for bleeding in univariate and multivariate analyses.**

Variable	Univariate analysis		Multivariate analysis			
			Main model <sup>a</sup>		Stepwise model <sup>b</sup>	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Antiplatelet drug therapy	3.44 (1.14-9.66)	0.021	4.13 (1.01-17.03)	0.044	5.16 (1.41-18.36)	0.010
Male gender	1.27 (0.42-3.56)	0.65	1.89 (0.48-7.19)	0.34	—	—
Age (per 5 years increase)	1.07 (0.93-1.24)	0.37	1.06 (0.86-1.32)	0.63	—	—
Age > 65	1.42 (0.51-4.07)	0.50	—	—	—	—
Platelet count (per 100 G.L <sup>-1</sup> increase)	0.44 (0.25-0.73)	0.002	0.57 (0.28-0.97)	0.08	0.59 (0.30-0.97)	0.08
Platelet count < 100 G.L <sup>-1</sup>	3.56 (0.80-11.5)	0.05	—	—	—	—
PT (per 10% increase)	0.76 (0.61-0.97)	0.020	0.93 (0.64-1.37)	0.70	—	—
PT < 50%	2.54 (0.39-9.47)	0.23	—	—	—	—
APTT ratio (per 1 unit increase)	3.18 (1.26-6.81)	0.006	2.72 (0.53-12.10)	0.20	3.23 (0.93-9.11)	0.038
Increased APTT ratio > 1.4	3.28 (1.01-9.39)	0.033	—	—	—	—
Creatinine Cl. < 60 L.min <sup>-1</sup>	1.87 (0.53-6.63)	0.304	—	—	—	—
Creatinine Cl. < 30 L.min <sup>-1</sup>	4.68 (1.01-16.60)	0.025	1.85 (0.33- 8.43)	0.45	—	—
Indication for pleural procedure (pneumothorax vs pleural effusion)	1.00 (0.23-3.18)	> 0.99	—	—	—	—
Department (intensive care vs respiratory medicine)	2.44 (0.86-6.79)	0.106	1.01 (1.94-5.81)	0.99	—	—
Pleural procedure						
Closed pleural biopsy	ref		ref		ref	
Chest tube insertion	1.91 (0.35-35.37)	0.54	0.59 (0.05-14.17)	0.69	—	—
Thoracentesis	1.73 (0.28-33.38)	0.62	0.93 (0.10-20.31)	0.96	—	—
Operator (junior vs senior physician)	2.43 (0.83-8.80)	0.13	—	—	—	—
Experience < 50 procedures	1.78 (0.63-5.76)	0.29	3.88 (0.91-27.01)	0.10	3.88 (0.96-26.06)	0.09
Radiographic guidance	0.83 (0.23-2.43)	0.74	0.94 (0.18-3.79)	0.93	—	—
Pleural device diameter > 14F	0.40 (0.06-1.51)	0.24	—	—	—	—

CI: confidence interval; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; APTT ratio: patient/control APTT ratio; Cl: clearance

<sup>a</sup> n = 826; AIC = 121.6; number of Fisher Scoring iterations = 8

<sup>b</sup> n = 826; AIC = 108.4; number of Fisher Scoring iterations = 8