CHEST

Safety of Thoracentesis and Tube Thoracostomy in Patients With Uncorrected Coagulopathy

A Systematic Review and Meta-analysis

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BACKGROUND: Thoracentesis and tube thoracostomy are common procedures with bleeding risks, but existing guidelines may be overly conservative. We reviewed the evidence on the safety of thoracentesis and tube thoracostomy in patients with uncorrected coagulopathy.

RESEARCH QUESTION: Is it safe to perform thoracentesis and tube thoracostomy in patients with uncorrected coagulopathy?

STUDY DESIGN AND METHODS: This systematic review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. PubMed and Embase were searched from inception through December 31, 2019. Included studies involved patients with uncorrected coagulopathy because of disease (eg, thrombocytopenia, liver cirrhosis, kidney failure) or drugs (eg, antiplatelets, anticoagulants). Relevant outcomes were major bleeding and mortality.

RESULTS: Eighteen studies (5,134 procedures) were included. Using random-effects meta-analysis, the pooled major bleeding and mortality rate was 0 (95% CI, 0%-1%). No publication bias was found. Excluding six studies that were in abstract form, meta-analysis of the remaining 12 full articles showed that the pooled major bleeding and mortality rate also was 0 (95% CI, 0%-2%). Subgroup analysis performed for patients with uncorrected coagulopathy resulting from disease or drugs showed similar results.

INTERPRETATION: Among patients with uncorrected coagulopathy who underwent thoracentesis or tube thoracostomy, major bleeding and mortality complications were uncommon. Our results suggest that in appropriately selected patients, thoracentesis or tube thoracostomy can be performed safely.

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KEY WORDS: bleeding complications; pleural effusion; pneumothorax; thoracentesis; thoracostomy

ABBREVIATION: INR = international normalized ratio

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Take-home Points

Study Question: Is it safe to perform thoracentesis and tube thoracostomy in patients with uncorrected coagulopathy?

Results: We systematically reviewed the evidence regarding patients with uncorrected coagulopathy resulting from disease or drugs who underwent thoracentesis or tube thoracostomy and found that the pooled major bleeding and mortality rate was 0 in 18 included studies (95% CI, 0%-1%).

Interpretation: It is most likely to be safe to perform thoracenteses and tube thoracostomy in select patients with uncorrected coagulopathy, which would prevent unnecessary correction or delay that may lead to adverse outcomes.

Thoracentesis[1] and tube thoracostomy[2] are common pleural procedures, but as invasive procedures, they both carry a risk of bleeding, such as hemothorax or hemoptysis, which can require blood transfusion or other interventions including embolization or surgery to address the complication.[3] At the same time, patients with coagulopathy resulting from disease or medications are encountered frequently. Puchalski et al[4] found that among 312 patients needing pleural procedures, 42% had one or more risk factors for bleeding. Because it is reasonable to think that patients with coagulopathy would be at elevated risk of bleeding from pleural procedures, guidelines regarding this topic tend to be conservative.

The British Thoracic Society pleural disease 2010 guidelines recommend that nonurgent pleural aspirations and chest drain insertions be avoided in anticoagulated patients until the international normalized ratio (INR) is less than 1.5 and that, where possible, any coagulopathy or platelet defect be corrected before chest drain insertion.[5] The guidelines also state that for elective chest drain insertion, warfarin should be stopped and time allowed for its effects to resolve. However, the guidelines do not specifically address the safety of pleural procedures when platelets are low or when patients are receiving antiplatelets.

The 2019 Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions acknowledge a lack of high-quality data to guide whether preprocedural laboratory testing reduces periprocedural bleeding risk.[6] In these guidelines, a low-bleeding risk procedure was defined to be one that is expected rarely to have hemorrhagic complications or one occurring in areas where bleeding is easy to diagnose and control. A nontunnelled chest tube placement for pleural effusions was classified as a low bleeding risk procedure. For low-bleeding risk procedures, the guidelines do not recommend routine checking of prothrombin time, INR, platelet count, or hemoglobin unless the patient is assessed to have an inherently higher bleeding risk. The thresholds provided are to correct the INR to the range of 2 to 3 and to transfuse if the platelet count is $<$ 20,000/μL. For thoracentesis, the guidelines acknowledge that the pooled data on patients with abnormal coagulation profiles indicate a very low risk of major bleeding and that the need for prophylactic blood products is questionable. In terms of drugs, the guidelines recommended that for low-bleeding risk procedures, antiplatelets and direct oral anticoagulants should not be withheld and that for patients receiving warfarin, an INR of $\leq$ 3 should be targeted.

Since the above guidelines have been published, several studies have demonstrated the safety of pleural procedures in patients with coagulopathy. If indeed the overall complication rates remain low, pleural procedures could proceed more expediently without further testing or correction of coagulopathy. Additionally, correction of coagulopathy with plasma or platelet transfusions carry risks, and avoidance of unnecessary correction could lessen patient harm.[7] We hypothesize that thoracentesis and tube thoracostomy have low ($<$ 3%) complication rates and that complications are relatively minor in patients with uncorrected coagulopathy. We therefore aimed to review systematically the available evidence to evaluate the safety of thoracentesis and tube thoracostomy in patients with coagulopathy.

Methods

Search Strategy and Selection Criteria

The study was registered with PROSPERO (Identifier: CRD42020152226) and was performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis guidelines.[8] Three authors (C. F., C. W. C. T., and D. K. Y. T.) independently and systematically searched PubMed and Embase for all relevant studies published from inception to December 31, 2019, using the patient, intervention, comparison and outcome search strategy[9] (e-Table 1). Studies were included if they reported rates of major bleeding (as defined by hemothorax, hemoptysis, bleeding requiring transfusion, or operation)

and death in patients who had undergone a pleural procedure (needle thoracentesis or tube thoracostomy) while having uncorrected coagulopathy (because of disease or drugs like antiplatelets and anticoagulants). Conference abstracts were included if they had the information required. Articles were excluded if they had an irrelevant topic, wrong patient type, wrong exposure, wrong analysis, or missing outcomes.

Data Extraction and Quality Assessment

Data extracted included the number of thoracenteses or tube thoracostomies, patient demographics, coagulopathy risk, major bleeding, and mortality. The included studies were assessed independently by two authors (C. W. C. T. and D. K. Y. T.) for risk of bias using the Risk of Bias in Non-randomised Studies of Interventions tool.[10] This tool comprises seven domains, namely, biases resulting from (1) confounding, (2) selection of participants, (3) classification of interventions, (4) deviations from intended intervention, (5) missing data, (6) measurement of outcomes, and (7) selection of reported results. Each study was evaluated based on the seven domains and determined to be at low, moderate, serious, or critical risk of bias. Studies that did not provide enough information to permit a judgement within a certain domain then were labelled as "no information." Disagreements between the two authors were resolved by discussion with a third author (C. F.).

Statistical Analysis

A random-effects model was used to estimate the pooled complication rates after a Freeman-Tukey double arcsine transformation to stabilize the variances. Statistical heterogeneity across studies was assessed with the I^2 statistic, and publication bias was evaluated with funnel plots and Egger test. All the analyses were carried out using Stata 13 software (StataCorp), and all tests were two-tailed with a significance level of .05.

Results

Study Selection

e-Figure 1 depicts the Preferred Reporting Items for Systematic Review and Meta-analysis flow chart of the literature search and article selection. Eleven thousand seven hundred sixty studies were identified through database searches and 777 duplicates were removed, leaving 10,983 studies. After assessment of title and abstract, 10,965 articles were excluded for irrelevant topic, wrong patient, wrong exposure, wrong analysis, or missing outcomes. The full texts of the remaining 18 articles were analyzed for eligibility. All 18 articles (12 full research articles and six conference abstracts) were included in the review and meta-analysis. The quality evaluation results are displayed in Table 1.[11-27]

Study Characteristics

The 18 studies included a total of 5,134 procedures (thoracentesis or chest tube insertions) from four different countries: 15 from the United States, one collaboration between the United States and the United Kingdom, one from France, and one from Italy. Characteristics of the included studies are shown in Table 2. Patients were enrolled from 1947 through 2019. All of these studies involved patients who showed an elevated INR, showed thrombocytopenia, were receiving anticoagulants or antiplatelets, or showed liver disease or chronic renal failure.

Study Outcomes

Major bleeding complications were noted in six studies, and included hemothorax, hemoptysis, hemoglobin drop of $>$ 2 g/dL, bleeding requiring transfusion, and bleeding requiring procedural intervention. However, major bleeding complications were rare, and meta-analysis showed that the pooled major bleeding and mortality rate was 0 (95% CI, 0%-1%) for all 18 included studies (Fig 1), and no evidence of publication bias was found (Fig 2). Excluding the six articles that were only in abstract form, meta-analysis of the remaining 12 full articles showed that the pooled major bleeding and mortality rate was similarly 0 (95% CI, 0%-2%) (e-Fig 2), and no evidence of publication bias was found (e-Fig 3). Subgroup analyses were performed for patients with drug-related bleeding risk only, thrombocytopenic risk only, and elevated INR risk only. Further subgroup analyses were performed in patients undergoing tube thoracostomy only and thoracentesis only as well as for retrospective studies and prospective studies only. The results of these are summarized in Table 3. The forest and funnel plots for the subgroup analyses can be found in e-Figures 4 to 17.

Discussion

Our systematic review found a low complication rate ($<$ 3%) for major bleeding (defined as hemothoraces, bleeding causing a hemoglobin drop of $>$ 2 g/dL, or bleeding requiring transfusion or procedural intervention) or mortality in patients with uncorrected bleeding tendencies who underwent thoracentesis or tube thoracostomy. These patients included those with INR of $>$1.5, platelets of $<$ 50,000/μL, chronic liver disease, or end-stage kidney failure and those receiving antiplatelets or anticoagulants. Subgroup analyses performed on the individual risk factors for bleeding similarly showed that major bleeding or mortality complications were uncommon. Results were consistent when subgroup analyses were performed for those who

TABLE 1] Risk of Bias Assessment of Included Studies Using the ROBINS-I Tool

Study Author(s) and Year	Bias Because of Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Because of Deviations From Intended Interventions	Bias Because of Missing Data	Bias in Measurement of Outcomes	Bias in Reporting of Data	Overall Risk of Bias
McVay and Toy[11] (1991)	Serious	Low	Low	Moderate	Serious	Low	Low	Serious
Argento et al[12] (2011)	NI	Low	Low	Low	Low	NI	Low	NI
Ault and Rosen[13] (2011)	NI	Low	Low	Low	Low	NI	Low	NI
Patel and Joshi[14] (2011)	NI	Low	Low	Low	Low	Low	Low	NI
Abouzgheib et al[15] (2012)	Serious	Low	Low	Low	Low	Low	Low	Serious
Irugulapati et al[16] (2012)	NI	Low	Low	Low	Low	NI	NI	NI
Zalt et al[17] (2012)	NI	Low	Low	Low	Low	Low	Low	NI
Dammert et al[18] (2013)	NI	Low	Low	Low	Low	Low	Low	NI
Hibbert et al[19] (2013)	NI	Low	Low	Low	Low	Low	Low	NI
Mahmood et al[20] (2013)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Puchalski et al[4] (2013)	Moderate	Moderate	Low	Low	Moderate	Low	Low	NI
Dangers et al[21] (2015)	NI	Low	Low	Low	Low	Low	NI	NI
Wooley et al[22] (2016)	NI	Low	Low	Low	Low	Low	Low	NI
Shojaee et al[23] (2018)	NI	Moderate	Low	Low	Low	Low	Low	NI
Orlandi et al[24] (2018)	NI	Low	Low	Low	Low	Low	Low	NI
Perl et al[25] (2018)	NI	NI	NI	NI	NI	NI	NI	NI

(Continued)

TABLE 1 *(Continued)*

Study Author(s) and Year	Bias Because of Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Because of Deviations From Intended Interventions	Bias Because of Missing Data	Bias in Measurement of Outcomes	Bias in Reporting of Data	Overall Risk of Bias
Navin et al[26] (2019)	NI	Low	Low	Low	Low	Low	Low	NI
Patel et al[27] (2019)	NI	Moderate	Low	Low	Moderate	Low	NI	NI

NI = no information; ROBINS-I = Risk of Bias in Non-randomised Studies of Interventions.

underwent tube thoracostomy only or thoracentesis only and when analyzing retrospective and prospective studies separately.

In a study by Hibbert et al,[19] thoracenteses were shown to be safe in patients with abnormal preprocedural coagulation parameters and that correcting these abnormalities did not provide any benefit. In cirrhotic patients, a study by Wooley et al[22] found that in 66 patients with cirrhosis who underwent thoracentesis, no significant bleeding complications occurred. The average INR was 1.6.

In a prospective study, Mahmood et al[28] compared 25 patients undergoing small-bore chest tube insertion while receiving clopidogrel vs 50 patients not receiving clopidogrel, and only one patient in the clopidogrel group demonstrated a hemothorax. In another prospective study, Zalt et al[17] performed 45 ultrasound-guided thoracentesis procedures in 30 patients receiving clopidogrel, and only one instance of a subcutaneous hematoma was found. Regarding ultrasound-guided thoracentesis in patients receiving novel oral anticoagulants, a retrospective analysis by Patel et al[27] showed that of 115 thoracentesis procedures, 103 patients either were receiving novel oral anticoagulants or clopidogrel, and no bleeding complications occurred.

Thoracentesis and tube thoracostomy seem to have a lower risk of bleeding complications than previously thought. This may be because of better training,[29] better safety practices,[30,31] and the use of ultrasound guidance.[32] These measures, together with the development of procedural teams and strict observance to clinical protocol, have allowed safe performance of thoracentesis on a broader range of patients without increased complications, including those with underlying bleeding risk.[33] A study of 19,339 thoracenteses showed that the use of ultrasound during thoracentesis reduced the likelihood of hemorrhage by 39%.[34] Similar studies for abdominal paracentesis also have found an overestimation of bleeding risk in patients with bleeding tendencies.[35]

Of relevance to the findings of our systematic review, Dangers et al[36] recently published a study that concluded that antiplatelet therapy was associated with an increased risk of bleeding and serious bleeding after a pleural procedure. Although it falls outside our study period (study end date, December 31, 2019), when we included this multicenter study into our pooled analysis for bleeding complications, we found that the major bleeding complication rate remained 0 (e-Fig 18). This is

TABLE 2] Characteristics of Included Studies

Study Author(s) and Year	Country	Study Type	Biodata: Mean age, y % Female Mean BMI	Bleeding Risk Factors: Medications Comorbidities Mean INR Mean Plt Mean Cr	Procedures: No., Description Indication	Procedurist Description	Outcomes: Major Bleeding Events, No. (%) Description
McVay and Toy[11] (1991)	United States	Retrospective	NR NR NR	Medications: NR Liver disease, NR; renal disease, 16.99%; receiving dialysis, NR; ventilator support, NR INR > 1.5 1% Plt < 50,000/μL, 10.5% Mean INR, NR Mean Plt, NR Mean Cr, NR	207 thoracenteses Indication: pleural effusion 207 of 608 procedures were thoracenteses	NR	19 (3.1%) 19 showed a Hb drop of > 2, 1 patient required transfusion; not specified which patients underwent paracentesis or thoracentesis
Argento et al[12] (2011)	United States	Retrospective (abstract)	NR NR NR	Aspirin, NR; clopidogrel, 1.9%; other antiplatelets, NR; warfarin, 3.8%; heparin, 5.71%; LMWH, NR; NOAC, NR; other medications, NR Liver disease, NR; renal disease, 17%; receiving dialysis, NR; ventilator support, NR INR > 1.5, 2.85% Plt < 50,000/μL, 6.67% Mean INR, NR Mean Plt, NR Mean Cr, NR	105 thoracenteses Indication, NR	NR	0
Ault and Rosen[13] (2011)	United States	Prospective (abstract)	NR NR NR	Aspirin, 25%; clopidogrel, 100%; other antiplatelets, 8%; warfarin, 4%; heparin, 4%; LMWH, 6%; NOAC, 0%; other medications, 3% Liver disease, NR; renal disease, 2%; receiving dialysis, NR; ventilator support, NR INR > 1.5, 13% Plt < 50,000/μL, 4% Mean INR, NR Mean Plt, NR Mean Cr, NR	1,000 thoracenteses Indication, NR	Procedures were performed according to established procedure center protocol	0

(Continued)

TABLE 2] *(Continued)*

Study Author(s) and Year	Country	Study Type	Biodata: Mean age, y % Female Mean BMI	Bleeding Risk Factors: Medications Comorbidities Mean INR Mean Plt Mean Cr	Procedures: No., Description Indication	Procedurist Description	Outcomes: Major Bleeding Events, No. (%) Description
Patel and Joshi[14] (2011)	United States	Retrospective	70 43.97 NR	Medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR INR > 1.5, 32.48%[a] Plt < 50,000/μL, 6.08[b] Mean INR, 1.53 Mean Plt, 247 Mean Cr, NR	1,076 thoracenteses Indication, pleural effusion	Board-certified radiologist (staff or fellow)	0
Abouzgheib et al[15] (2012)	United States	Retrospective	73.1 55.6% NR	Aspirin, NR; clopidogrel, 100%; other antiplatelets, NR; warfarin, NR; heparin, NR; LMWH, NR; NOAC, NR; other medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR INR > 1.5, NR Plt < 50,000/μL, NR Mean INR, NR Mean Plt, NR Mean Cr, NR	24 thoracostomy Indication, pleural effusion (n = 22), pneumothorax (n = 2)	One of two interventional pulmonologists	0
Irugulapati et al[16] (2012)	United States	Retrospective (abstract)	NR	Aspirin, NR; clopidogrel, 100%; other antiplatelets, NR; warfarin, NR; heparin, NR; LMWH, NR; NOAC, NR; other medications, NR Liver disease, NR; renal disease, 71.42%; receiving dialysis, NR; ventilator support, NR INR > 1.5, NR Plt < 50,000/μL, NR Mean INR, NR Mean Plt, NR Average Cr, NR	7 thoracenteses Indication, NR	NR	0

(Continued)

TABLE 2] *(Continued)*

Study Author(s) and Year	Country	Study Type	Biodata: Mean age, y % Female Mean BMI	Bleeding Risk Factors: Medications Comorbidities Mean INR Mean Plt Mean Cr	Procedures: No., Description Indication	Procedurist Description	Outcomes: Major Bleeding Events, No. (%) Description
Zalt et al[17] (2012)	United States	Prospective	75.5 70% NR	Aspirin, NR; clopidogrel, 100%; other antiplatelets, NR; warfarin, NR; heparin, NR; LMWH, NR; NOAC, NR; other medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR INR > 1.5, 0 Plt < 50,000/μL, 0 Mean INR, NR Mean Plt, NR Mean Cr, NR	45 thoracenteses Indication, pleural effusion	Interventional pulmonology attending physicians and interventional pulmonology fellows; ultrasound guidance (SonoSite) used in all procedures	0
Dammert et al[18] (2013)	United States	Retrospective	71 30% 28	Aspirin, 91%; clopidogrel, 100%; other antiplatelets, NR; warfarin, NR; heparin, NR; LMWH, NR; NOAC, NR; other medications, NR Liver disease, NR; renal disease, 20.9%; receiving dialysis, NR; ventilator support, NR INR > 1.5, 2.33% Plt < 50,000/μL, 0 Mean INR, NR Mean Plt, NR Mean Cr, NR	43 thoracostomy Indication, pleural effusion (n = 40), pneumothorax (n = 3)	Pulmonary and critical care fellow under the supervision of an interventional pulmonologist	0
Hibbert et al[19] (2013)	United States	Retrospective	68 48% NR	Medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR INR > 1.5, 88% Plt < 50,000/μL, 17 Average INR, 1.9 Average Plt, 211 Average Cr, NR	706 thoracentesis Indication, NR	NR	0

(Continued)

TABLE 2] *(Continued)*

Study Author(s) and Year	Country	Study Type	Biodata: Mean age, y % Female Mean BMI	Bleeding Risk Factors: Medications Comorbidities Mean INR Mean Plt Mean Cr	Procedures: No., Description Indication	Procedurist Description	Outcomes: Major Bleeding Events, No. (%) Description
Mahmood et al[20] (2013)	United States	Prospective	70.2 16% 25.3	Aspirin, 88%; clopidogrel, 100%; other antiplatelets, NR; warfarin, NR; heparin, 0%; LMWH, 0%; NOAC, NR; other medications, NR Liver disease, NR; renal disease, 12%; receiving dialysis, NR; ventilator support, NR INR > 1.5, NR Plt < 50,000/μL, NR Mean INR, 1.16 Mean Plt, 278 Mean Cr, 159	17 thoracenteses 8 thoracostomies Indication, NR	Interventional pulmonology attending physicians or by fellows under direct faculty supervision	1 (4%) Hemothorax
Puchalski et al[4] (2013)	United States	Prospective	68.6 46% 26.9	Aspirin, NR; clopidogrel, 12%; other antiplatelets, NR; warfarin, NR; heparin or LMWH, 11%; NOAC, NR; other medications, NR Liver disease, NR; renal disease, 31%; receiving dialysis, NR; ventilator support NR INR > 1.5, 34% Plt < 50,000/μL, 12% Mean INR, NR Mean Plt, NR Mean Cr, NR	130 thoracenteses Indication, pleural effusion	Performed by a physician or physician assistant using ultrasound guidance	1 (0.77%) Underwent thoracotomy with decortication after thoracentesis for an empyema, bled 300 mL during surgery and received 4 units of fresh frozen plasma and 3 L of intravenous fluids during surgery
Dangers et al[21] (2015)	France	Prospective (abstract)	73 11% NR	Medications, NR Liver disease, NR; renal disease, 42%; receiving dialysis, NR; ventilator support, NR INR > 1.5, NR Plt < 100,000/μL, 7.5% Mean INR, NR Mean Plt, NR Mean Cr, NR	1,133 pleural procedures (pleural biopsies, chest tube insertions, thoracentesis) Indication, NR	8 respiratory care departments and 11 medical ICUs	5 (2.7%) Includes hemothorax, hematoma, and hemoptysis, but breakdown of numbers uncertain

(Continued)

TABLE 2] *(Continued)*

Study Author(s) and Year	Country	Study Type	Biodata: Mean age, y % Female Mean BMI	Bleeding Risk Factors: Medications Comorbidities Mean INR Mean Plt Mean Cr	Procedures: No., Description Indication	Procedurist Description	Outcomes: Major Bleeding Events, No. (%) Description
Wooley et al[22] (2016)	United States	Retrospective (abstract)	NR NR NR	Medications, NR Liver disease, 100%; renal disease, NR; receiving dialysis, NR; ventilator support, 0% INR > 1.5, NR Plt < 50,000/μL, NR Mean INR, 1.6 Mean Plt, NR Mean Cr, NR	66 thoracenteses Indication, NR	NR	0
Shojaee et al[23] (2018)	United States, United Kingdom	Retrospective	57 35.4% NR	Medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR INR > 1.5, NR Plt < 50,000/μL, NR Average INR, 1.7 Average Plt, 118.9 Average Cr, 132	274 thoracenteses Indication, pleural effusion	9 attending physicians, 261 postgraduates year 4-7, 4 unknown	5 (1.8%) Hemothorax
Orlandi et al[24] (2018)	Italy	Retrospective	70.8 10% NR	Medications, NR Liver disease, 0%; renal disease, 0%; receiving dialysis, 0%; ventilator support, NR INR > 1.5, 0% Plt < 50,000/μL, 100% Mean INR, NR Mean Plt, NR Mean Cr, NR	41 thoracenteses Indication, pleural effusion	5 experienced physicians[c] of the department	(0.69%) Bleeding only occurred in those without ultrasound guidance; no events when ultrasound was used
Perl et al[25] (2018)	United States	Retrospective (abstract)	NR NR NR	Aspirin, 46.6%; clopidogrel, 100%; other antiplatelets, NR; warfarin, 2.27%; heparin, 0%; LMWH, NR; NOAC, 2.27%; other medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR	88 thoracenteses Indication, pleural effusion	NR	0

(Continued)

TABLE 2] *(Continued)*

Study Author(s) and Year	Country	Study Type	Biodata: Mean age, y % Female Mean BMI	Bleeding Risk Factors: Medications Comorbidities Mean INR Mean Plt Mean Cr	Procedures: No., Description Indication	Procedurist Description	Outcomes: Major Bleeding Events, No. (%) Description
				INR > 1.5, NR Plt <50,000/μL, NR Mean INR, NR Mean Plt, NR Mean Cr, NR			
Navin et al[26] (2019)	United States	Retrospective	62 42.22% NR	Aspirin, NR; clopidogrel, 4.08%; other antiplatelets, NR; warfarin, NR; heparin, NR; LMWH, NR; NOAC, NR; other medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR: ventilator support, NR INR > 1.5, 100% Plt < 50,000/μL, 0% Mean INR, 2.3 Mean Plt, NR Mean Cr, NR	49 thoracostomies Indication, pleural effusion (n = 23), pneumothorax (n = 26)	Ultrasound-guided procedures by interventional radiologists or pulmonologist, CT-guided procedures by interventional radiologist	0
Patel et al[27] (2019)	United States	Retrospective	NR 27.8% NR	Aspirin, 0%; clopidogrel, 60%: other antiplatelets, 2.6%; warfarin, 0%; heparin, 2.61%: LMWH, NR; NOAC, 37.4%; other medications, NR Liver disease, NR; renal disease, NR; receiving dialysis, NR; ventilator support, NR INR > 1.5, NR Plt < 50,000/μL, NR Mean INR, 1.5 Mean Plt, 249 Mean Cr, 154.7	115 thoracenteses Indication, pleural effusion	Experienced interventional pulmonologists and radiologists, and trainees (fellows and residents) under direct supervision	0

Major bleeding events are defined as hemothorax, hemoptysis, hemoglobin drop of > 2 g/dL or requiring transfusion, or bleeding requiring surgical intervention. Cr = creatinine; Hb = hemoglobin; INR = international normalized ratio; LMWH = low molecular weight heparin; NOAC = novel oral anticoagulant; NR = not reported; Plt = platelets.

[a]Two hundred sixty-seven with INR > 1.5 of 822 procedures with available INR.

[b]Fifty-eight with platelets < 50,000/μL of 953 procedures with available platelet data.

[c]Routinely perform thoracentesis and had performed more than 200 procedures with and without ultrasound guidance.

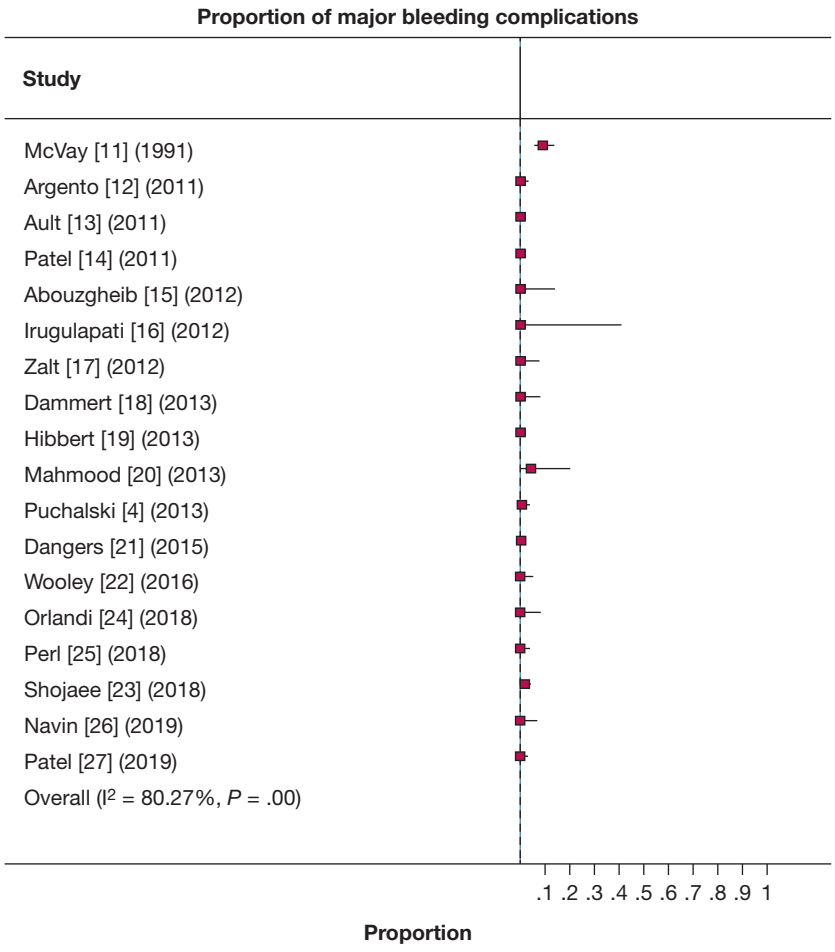

Figure 1 – *Forest plot showing major bleeding complications (all studies, n = 18). Heterogeneity $\chi^2 = 86.17$ (degrees of freedom, 17);* P = .00. *I^2 (variation in ES attributable to heterogeneity) = 80.27%. Estimate of between-study variance $\tau^2 = 0.02$. Test of ES = 0; z = 0.62;* P = .53. *ES = effect estimate.*

likely because although the study population was large (n = 1,124), only 186 patients were receiving antiplatelets. Looking at the study characteristics, the patients receiving antiplatelets in this study also experienced more renal failure, and thus would be at a higher risk of bleeding. Also relatively less use of image guidance (< 80%) and a higher percentage of junior operators (> 50%) was noted. The 24-h incidence of bleeding was 1.33% (95% CI, 0.71%-2.05%) in the entire population, 3.23% (95% CI, 1.08%-5.91%) in the antiplatelet group, and 0.96% (95% CI, 0.43%-1.60%) in the control group. The 95% CI of bleeding incidence in the antiplatelet group and control group overlapped. Similarly, the serious bleeding incidence of both groups also overlapped: serious bleeding incidence was 0.71% (95% CI, 0.27%-1.25%) in the overall study group, 2.69% (95% CI, 0.54%-5.38%) in the antiplatelet group, and 0.32% (95% CI, 0%-0.75%) in the control group. In the overall population, the study found a low rate of severe bleeding at 0.71% (95% CI, 0.27%-1.25%), with no mortality, which is consistent with our findings of 0 mortality in our systematic review. Dangers et al acknowledge that bleeding risk may be considered acceptable when balanced with the risk of a serious

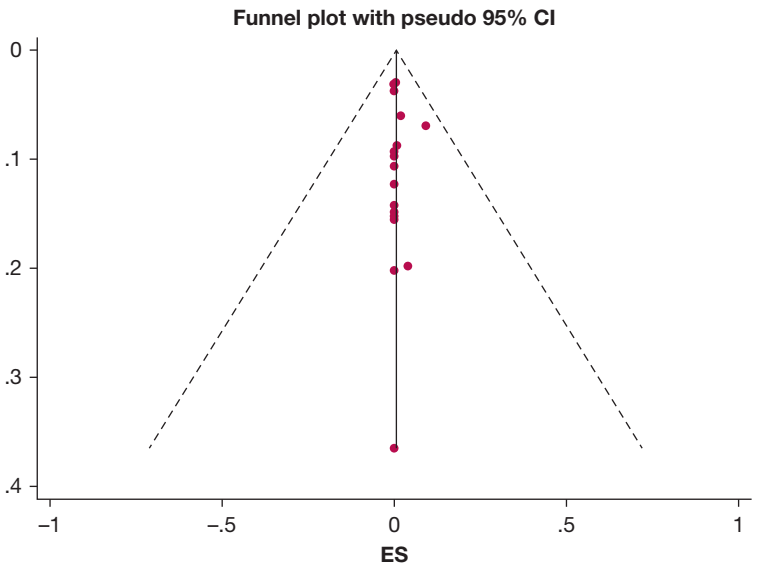

Figure 2 – *Funnel plot for all studies (n = 18). Egger's test for small-study effects,* P = .484. *ES = effect estimate.*

cardiovascular event associated with antiplatelet drug withdrawal in patients at high risk of thrombosis, and we agree that a personalized approach should be taken. We agree with Dangers et al's conclusions that the rates of bleeding and severe bleeding were low, indicating that pleural procedures may be performed with acceptable risk when antiplatelet therapy cannot be interrupted.

Collectively, the results of this systematic review suggest that thoracentesis and tube thoracostomy may be safe to perform in patients with uncorrected bleeding tendencies. Existing concerns regarding bleeding risk in this patient group may lead to an unnecessary delay in performing these procedures. In addition, testing for and unnecessarily correcting bleeding tendencies have their own downsides. For example, administering fresh frozen plasma or platelets to correct abnormal laboratory values exposes patients to the risks of transfusion of blood products.[37] Moreover, withholding antiplatelets or anticoagulants before a procedure may increase the risk of thrombotic events unnecessarily. In patients receiving clopidogrel for coronary stents, premature discontinuation of clopidogrel is associated with an increased risk of thrombosis[38] and myocardial infarction[39] and an increase in overall mortality.[40]

Although the total number of studied procedures was substantial (n = 5,134), this review has certain limitations. Only five of 18 of the included studies were prospective studies, and some of the included studies had imperfections leading to a risk of bias. In addition, most of the studies included were observational studies. The Risk of Bias in Non-randomised Studies of Interventions tool revealed that the overall risk of bias was serious in two studies and moderate in one study, although the remaining 15 studies generally showed low

TABLE 3] Subgroup Analyses of Bleeding Complications

Subgroup	No. of Studies	Pooled Results of Major Bleeding Complication Rates (95% CI)	I^2, %	*P* Value for Test of Heterogeneity	*P* Value for Egger's Test
Drug-related risks only	6	0 (0%-0%)	0.00	.59	.449
Thrombocytopenic risk only	1	0 (0%-9%)	NA	NA	NA
Elevated INR risk only	1	0 (0%-5%)	NA	NA	NA
Tube thoracostomy only	3	0 (0%-2%)	0.00	.97	NA
Thoracentesis only	13	0 (0%-1%)	85.16	.00	.526
Retrospective studies only	13	0 (0%-1%)	83.78	.00	.728
Prospective studies only	5	0 (0%-1%)	66.10	.02	.281

INR = international normalized ratio; NA = not applicable.

risks of bias in the assessable domains. Another limitation we recognize is the heterogeneity of the studies included, ranging from patients who were thrombocytopenic, those with elevated INR, and those who were receiving antiplatelets and anticoagulants. In addition, the analysis was performed in patients who underwent either thoracentesis or tube thoracostomy, as well as the inclusion of both retrospective and prospective studies. We have attempted to overcome this by performing subgroup analyses of patients with drug-related risk only, thrombocytopenic risk only, elevated INR risk only, tube thoracostomy only, thoracentesis only, retrospective studies only, and prospective studies only. The results of these are consistent with the analysis performed for all 18 included studies (e-Figs 4-17).

Interpretation

To conclude, in our review on the safety of thoracentesis and tube thoracostomy in patients with bleeding tendencies, the pooled complication rate of major bleeding and mortality was low. This study suggests that in appropriately selected patients with bleeding tendency, thoracentesis or tube thoracostomy can be performed safely. Our results support the Society of Interventional Radiology 2019 Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions—Part II guidelines, which state that thoracentesis and nontunnelled chest tube insertion for pleural effusions are low-bleeding risk procedures for which routine preprocedural checks of INR, hemoglobin, or platelet count are not recommended. In light of the growing evidence supporting the safety of thoracentesis and chest tube insertion in patients with bleeding tendency and the potential benefits of promptly performing pleural procedures while avoiding unnecessary coagulopathy correction, a review of guidelines that addresses more recent studies is needed.

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