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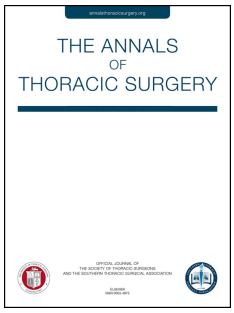

Randomized Controlled Trial of Thresholds for Drain Removal After Anatomic Lung Resection

Konstantinos Gioutsos, MD, Lasse Ehrenreich, Luis Filipe Azenha, MD, Christopher Siegbert Quapp, MD, Gregor Jan Kocher, MD, Jon Andri Lutz, MD, Stephan Peischl, PhD, Patrick Dorn, MD

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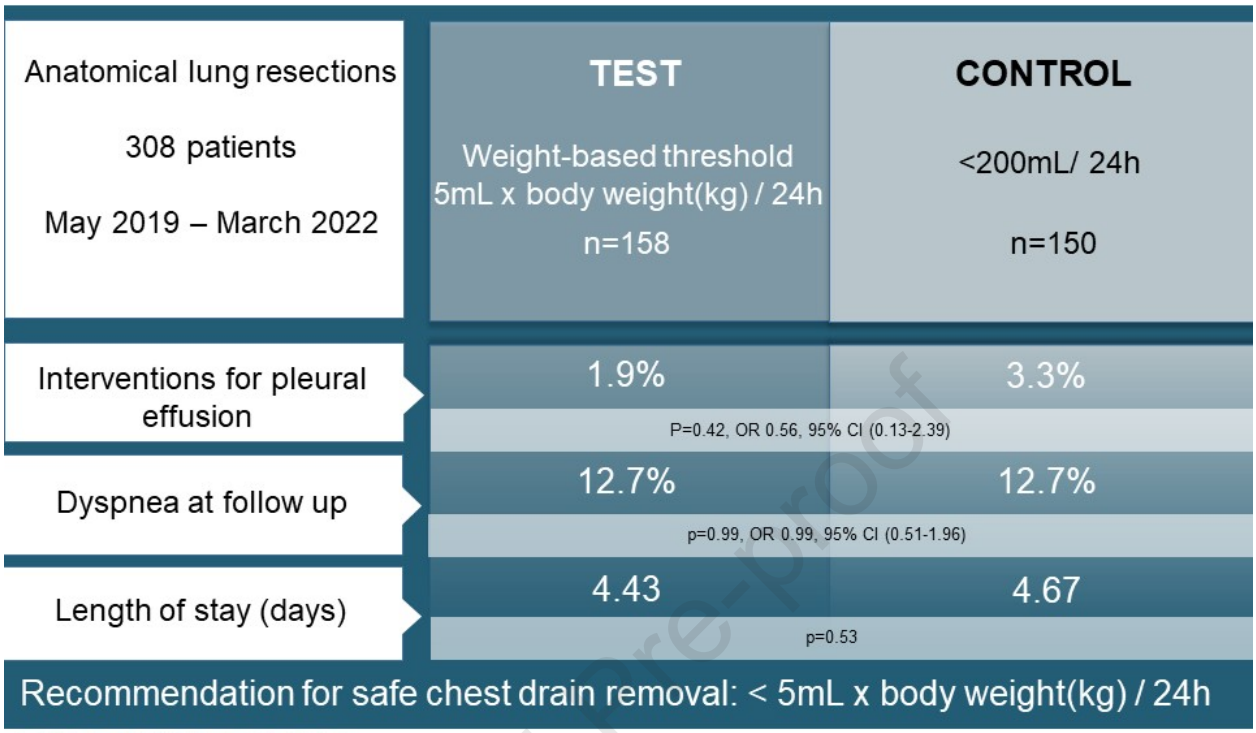
Weight-adjusted Fluid Threshold for Safe Chest Drain Removal After Lung Surgery



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Randomized Controlled Trial of Thresholds for Drain Removal After Anatomic Lung Resection

Running head: Chest drain removal after lung resection

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ABSTRACT

BACKGROUND: The criteria for chest drain removal following lung resections remain vague and rely on personal experience instead of evidence. Since pleural fluid resorption is proportional to body weight, a weight-related approach seems reasonable. We examined the feasibility of a weight-adjusted fluid output threshold concerning postoperative respiratory complications and the occurrence of symptomatic pleural effusion after chest drain removal. Our secondary objectives were the length of hospital stay and the pain levels before and after chest drain removal.

METHODS: Single-center randomized controlled trial including 337 patients planned for open or thoracoscopic anatomical lung resections. Patients were randomized postoperatively into two groups. The chest drain was removed in the study group according to a fluid output threshold calculated by the 5 mL x body weight (in kg) / 24 hours formula. In the control group, our previous traditional fluid threshold of 200 mL/ 24 hours was applied.

RESULTS: No differences were evident regarding the occurrence of pleural effusion, dyspnea at discharge and 30 days postoperatively. In the logistic regression analysis, the surgical modality was a risk factor for other complications, and age was the only variable influencing postoperative dyspnea. Time to chest drain removal was identical in both groups, and time to discharge was shorter following open surgery in the test group.

CONCLUSIONS: No increased postoperative complications occurred with this weight-based formula, and a trend toward earlier discharge after open surgery was observed in the test group. Registered as clinical trial NCT03093610 on ClinicalTrials.gov (https://clinicaltrials.gov/)

The timing of chest drain removal after pulmonary resections is crucial in the era of Enhanced Recovery after Surgery (ERAS) [1]. Since removing the chest drain is a relief for the patient, as it is associated with improving pain and promoting mobilization, it is of great interest to determine the earliest possible time to do so without taking any additional risks [2]. Drainage management also directly impacts hospital discharge planning, thus the healthcare system requires the most efficient standardized protocol possible [3].

Chest drain management and the volume threshold for removal after pulmonary resection remain controversial, as most thoracic surgeons rely on personal experience and institutional policy rather than evidence. The decision to remove the chest drain is based on the absence of air leakage, densely bloody, purulent, or chylous pleural effusion, and a reduced volume of fluid drained. Over the last decade, a significant upward adjustment has been observed regarding the quantity of drainage. Several randomized controlled trials (RCT) have already addressed the `appropriate fluid volume' parameter for safe drain removal [4-8].

Considering the most recent studies, seeing that we could move away from the traditional low-limit values has been gratifying. However, adopting a fixed or unlimited value that ignores the physiological dependence of pleural fluid turnover on body weight seems inappropriate [2]. Miserocchi recognized the corresponding relationship as early as 1997 [9]. An excessive increase in pleural filtration rate is considered to cause pleural effusions with decreased absorption potential. Extensive or progressive pleural effusions require intervention and, if clinically relevant, must be treated by thoracocentesis or reinserting a chest drain.

This study aimed to investigate whether a weight-adjusted fluid threshold for chest drain removal is appropriate as a physiologic approach without an increased risk of pleural effusions associated with the need for repeat drains (primary objective). We also aimed to investigate the impact of this adapted management on drainage duration, length of hospital stay, and patient discomfort (secondary objectives). The preliminarily specified hypothesis was that a body-

weight-based approach would allow earlier chest drain removal without increasing complication rates.

PATIENTS AND METHODS

Participants and Study Design

Adult patients undergoing elective open or minimally-invasive (uniportal) anatomical lung resection were recruited. Exclusion criteria were planned pneumonectomy, non-anatomical lung resection, preoperative infections such as pleural empyema, chest wall resections, additional planned mechanical or chemical pleurodesis, and pregnancy. In addition, patients with poor compliance (i.e., due to severe forgetfulness, cognitive impairment, psychiatric diagnoses, decreased ability or willingness to follow instructions) were not included. Patients who required surgical revision during hospitalization, for example, because of persistent air leakage or significant bleeding, were excluded from the final analysis. Further exclusion criteria included complications such as discharge with a chest drain in situ due to persistent air leakage, chylothorax, or death.

Ethics Approval, Registration and Reporting

This randomized controlled trial was approved by the Ethics Committee in Bern, Switzerland, on April 4, 2019 (2017-00527) and registered as clinical trial NCT03093610 on ClinicalTrials.gov (https://clinicaltrials.gov/). Written informed consent was obtained from all patients for this study. The study design was reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consort-statement.org) and international statistical

guidelines. (Supplemental Figure 1) The study is conducted in accordance with the protocol and principles of the current version of the Declaration of Helsinki and the guidelines for good clinical practice (GCP) issued by the ICH, if medical devices are involved: European Medical Devices Directive 93/42/EEC and ISO standards 14155 and 14971, Swiss law and the requirements of the Swiss regulatory authorities.

Randomization

Candidates were randomly assigned to either the test group or the control group. The study nurse informed the surgical team only after the patient was admitted to the post-anesthesia care unit. The assignment sequence was previously established by a research consultant using block randomization from www.sealedenvelope.com, and the investigators were blinded. The study period began with the randomization of the first patient and ended on the day of clinical follow-up in the thoracic surgery consultation of the last patient approximately 4 weeks after discharge.

Standard Treatment

All surgeries were performed in the presence of a board-certified thoracic surgeon via a standardized uniportal approach or anterolateral muscle-sparing thoracotomy. The bronchovascular structures were divided separately, applying endostaplers.

Regardless of the surgical access chosen, systematic mediastinal lymph node dissection was performed in all patients with lung cancer. This was not necessarily the case for secondary malignancies or benign lesions. After minimally-invasive procedures, one 24-French chest drain towards dorsoapical was placed. After open procedures, two 24-French thoracic drains were passed through 2 additional incisions made 2 to 3 intercostal spaces lower than the thoracotomy. One "air drain" was placed ventroapically, and the second "fluid drain" dorsobasal.

Suction of -5 cm H_20 was applied to the drains in the immediate postoperative period for 24 hours. The suction was then reduced on the electronic chest drain system to -1 cm H_20 on postoperative day 1, if the patient tolerated it from a respiratory point of view and no progressive subcutaneous emphysema was observed.

The pleural fluid drainage rate was recorded by the study nurse at the daily morning rounds and after the patient was mobilized for the first time postoperatively. If the criteria were met, the chest drain was removed. After removal, a chest x-ray was performed to assess lung expansion and to rule out pneumothorax or pleural effusion.

The follow-up period was divided into two phases:

1. the inpatient period began after surgery and lasted until discharge.

2. the out-of-hospital period began immediately after discharge and lasted until the postoperative appointment in our outpatient clinic 4 weeks after discharge. During this time, the patient regularly consulted the primary care physician. In case of abnormalities, our on-call physician was contacted to decide on further action depending on the urgency of the complaint.

After the first postoperative follow-up appointment, further follow-up care was provided as appropriate.

Test Group. Total body lymph flow is estimated at 1 mL/ kg body weight/hour. According to physiological analyses by Miserocchi et al. (1997), the maximum pleural lymphatic absorption in the pleural space is about 40% of the total body lymph flow. Assuming a safe pleural absorption of 20%, the turnover is 0.2 mL/ kg body weight/hour or 5 mL/ kg over 24 hours. This yields the simplified formula body weight x 5 = pleural fluid production/ 24 hours. Thus, in the experimental group of patients, the chest drain would be removed as soon as the amount of fluid (mL/ 24h) is

less than the body weight (in kilograms) multiplied by 5, assumed that there is no air leakage and the quality of the drained fluid did not suggest chylous or bloody effusion. In cases of doubt, laboratory analyses were performed for confirmation (i.e., relevant hemoglobin drop in case of blood or increased lipids in case of chylothorax).

Control Group. The chest drain management in the control group is performed according to our previous traditional protocol. This means that the drain can be removed when the pleural fluid drainage rate reaches 200 mL/ 24h or less, air leakage has ceased, and fluid quality is unremarkable.

Differences Between Interventions. Fluid volume is the only intervention-difference between the two groups. Complete blinding did not have to be attempted, as the flow rate reading was taken by individuals not involved in the study, and the drain removal was performed by independent ward physicians.

Data Collection, Study Outcomes, and Definitions

Patient characteristics were described using the hospital's electronic medical record system data. The primary outcome was symptomatic pleural effusion after chest drain removal. Symptomatic was defined as the presence of dyspnea with radiologically verified pleural effusion. For example, persistent oxygen demand or deterioration of respiratory condition during the perioperative hospital stay were reasons for further radiological examinations or other investigations. At the first follow-up visit in our thoracic surgery consultation, all patients completed a dyspnea questionnaire, based on which further actions were taken. The time of

chest drain removal was recorded in the patient's electronic medical record. Pain and other symptoms were repeatedly assessed with standardized tests (i.e., visual analog scale (VAS) before and after chest drain removal). The study nurse recorded these scores daily and documented them continuously in the electronic medical record. Postoperative discharge timing was determined by both objective medical factors and subjective patient factors. Delays in discharge for non-medical reasons were noted.

Sample Size Calculation and Statistical Analyses

The study was a randomized controlled non-inferiority trial. Participants were randomly assigned into two groups with block sizes of 4, 6, and 8.

To achieve a power of 80%, we needed a total of 304 participants. This number was calculated using a normal approximation for the standard deviation of the differences between the two groups with the following parameters:

1. significance level: 5%

2. power (1-beta): 80%

3. percentage of symptomatic pleural effusions in the control group: 2%

4. percentage of symptomatic pleural effusions in the test group: 2%.

5. threshold for non-inferiority, d: 4%.

We compared all numerical variables between the two groups using t-tests (Figure 1, Table 1). Confidence intervals for odds ratios for categorical variables were calculated using the Wald-method, and p-values were obtained using Chi-squared tests. We fitted logistic regression

models to predict factors influencing the risk for complications and performed automatic backward selection using the Akaike Information Criterion (AIC).

RESULTS

Between May 8, 2019, and March 10, 2022, 337 patients planned for open (anterolateral thoracotomy) or minimally-invasive (uniportal thoracoscopic-assisted) anatomical lung resection met the primary inclusion criteria for the study and consented to participate. They were randomly assigned to either the test group (n=170) or the control group (n=167). Complete data from all randomized patients were analyzed.

A total of 29 patients had to be excluded from the final data analysis because they met the secondary exclusion criteria. One patient had to be converted to pneumonectomy because of the intraoperative tumor situation. Furthermore, three patients died from postoperative complications during hospital stay while their chest drain was still in situ. Two patients developed a chylothorax and were excluded. Four patients were excluded due to re-operation, three for persistent air leakage and one for empyema. 19 patients were discharged home with the chest drain still in place because of a persistent air leak that did not spontaneously cease during hospitalization. All excluded cases corresponded to scenarios where we either had no data on complications or where neither of the two treatments could be applied.

After subtracting these 29 patients, 308 were included in the final analysis, 158 in the test group and 150 in the control group. Patients were homogeneously distributed in both groups with respect to age, weight and pain situation before and after chest drain removal (Figure 1, Table 1). Furthermore, the distribution of surgical modalities in terms of lobectomy, segmentectomy, minimally-invasive, and open, was comparable between the two groups. (Table 1) Differences in

the amount of drainage over the last 24 hours at the time of chest drain removal are shown in Figure 2.

There were no significant differences in the incidence of pleural effusion between the two groups. The re-intervention rate for symptomatic pleural effusion, defined as the need for thoracocentesis, pigtail drainage, or chest drain insertion, was 1.9% in the test group and 3.3% in the control group.

Dyspnea or worsening dyspnea at discharge and at the 4-week follow-up was also similar in the 2 groups. (Table 2)

Moreover, pneumonia during or after hospitalization, other non-respiratory complications, and interventions for pneumothorax or emphysema were also comparable between groups. (Table 3)

To identify any factors - including the treatment group - that might affect the risk of complications, we fitted logistic regression models to predict the risk for pleural effusions, respiratory complications, or other complications from the recorded variables. Logistic regression allows us to obtain odds ratios while controlling for more than one explanatory variable and analyzing the association of all variables together. No variable had a significant effect on the occurrence of pleural effusion (Supplemental Tables 1 and 2). Time to chest drain removal was identical in both groups, with a mean of 3.06 days in the test group and 3.14 days in the control group (P = 0.87). Time to hospital discharge was also comparable in both groups (4.67 and 4.43 days in the control and the test group, respectively, P = 0.53). (Figure 3)

Another interesting finding was that many patients in the test group had a drainage volume of less than 200 mL in the 24 hours before chest drain removal, which is actually the cut-off value for the control group. (Figure 2). Removing these individuals from the analysis should theoretically amplify any observable differences between the groups, however, at the cost of

power to detect statistical significance due to the smaller sample size. We repeated the analysis without these 81 individuals in the test group. Interestingly, the odds ratios for all complications decreased (Table 4), suggesting that our formula might actually reduce the risk of complications.

COMMENT

Most thoracic surgeons place chest drains after anatomic lung resections for postoperative intrathoracic monitoring and to avoid secondary acute complications such as tension-pneumothorax or symptomatic fluid retention. Since removing the chest drain is associated with improving the pain situation and promoting a better mobilization of the patient, there is interest in removing the chest drain as early as possible [10, 11].

Moreover, it has been shown that the respiratory function in terms of forced expiratory volume in the first second (FEV1) improved by 13% directly after chest tube removal. [12]

The fluid drainage threshold below which the chest drain removal is considered appropriate remains a point of contention. A safe threshold should minimize the likelihood of chest drain reinsertion for symptomatic fluid accumulation following chest drain removal.

Current practice varies strongly among countries, institutions, and surgeons. Although most general thoracic surgeons utilize a cut-off value of 100-300 mL non-hemorrhagic, non-chylous pleural fluid per day, these values are rather based on experience than evidence.

The focus of previous studies has been on a standard threshold that is independent of patient size and weight. On the one hand, various fixed threshold values have been taken, and on the other hand, attempts have been made to dispense with a threshold value altogether and to

remove the chest drain regardless of the volume of fluid drained. However, the latter showed that immediate intervention, such as a new chest drain or thoracocentesis, was necessary for almost 10% of patients [13]. One RCT used three different thresholds of 150, 300, and 450 mL/ d and found that 300 mL/ d was the highest threshold with an acceptable risk of pleural effusion occurrence [14]. However, these studies had in common that the monitoring time was focused on hospitalization with no further follow-up period.

Lack of sample size calculations and not strictly adhering to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines is a weakness in many studies. However, reviewing the literature on this topic, it is generally clear that the threshold for 24-hour drainage considered safe for chest drain removal has steadily increased over the past 15 years [15].

These efforts should also impact hospital profitability by reducing hospital length of stay and, thus, hospital costs. Our formula for determining the amount of fluid drained via a chest drain, adjusted for body weight, had no demonstrable disadvantage in the incidence rate of complications.

A recent prospective randomized trial [16] investigated the formula of 5mL/ kg/ day as a new threshold for chest drain removal. 80 patients following VATS lobectomy were assigned into 2 groups. A `standard` threshold of 250 mL/ day in the control group, whereas in the test group, the 5 mL/ kg/ day formula was applied. A statistically significant shorter length of hospital stay was shown and the re-intervention rate was similar between the 2 groups; however, the study was underpowered for the second observation. With this randomized controlled trial, we demonstrated that weight-adjusted fluid volume calculation (body weight multiplied by a factor of 5) over 24 hours is a physiologic approach that can be used for chest drain removal without increasing the risk for pleural effusion.

Almost half of the patients in the test group fulfilled the criterion of 200 mL/ 24 hours on the removal day. So theoretically, half of the patients in the test group `profited` from the higher threshold value accepted in their group by having their chest drain removed earlier. Unfortunately, and mainly due to outliers, this difference in the time of removal was not translated into the results. Furthermore, the overall complication rate in the test group was not higher than in the control group. Of note, in the thoracotomy sub-group, there was a clinically significant shorter time to discharge among the test group patients compared with the control group.

Most studies over the last years examining potential new thresholds for chest drain removal were selective, excluding many patients according to their body mass index (BMI) or different reception. [15] The most recent ones examined VATS procedures [7,15].

Limitations

Our study has limitations, the most important being the diversity of the procedures included. Our cohort included patients independent of the surgical technique (minimally-invasive uniportal to open). One might assume that the chest wall trauma caused by the thoracotomy and the volume defect following a lobectomy vary significantly compared to segmentectomy. These essential factors might affect the intrapleural pressure difference and eventually the pleural fluid production, therefore the drainage over the chest drain. However, we attempted to find a formula that could be applied following any anatomical lung resection without considering the surgical modality and the extent of lung resection.

Another aspect that should be addressed is that the threshold of 5 mL/ kg/ 24h might be underestimated. The calculations were based on physiological observations, but the presence of a plastic tube as foreign body in the pleural space of a recently operated patient applying

active suction would promote the production of pleural fluid. Disruption of the balance between production and absorption by the pleural surface would likely result in an increased rate of pleural fluid drainage. This observation could be the subject of a further study. Another direction might be to focus more on the quality of the drained fluid rather than the quantity.

Another possible co-founder is overweight patients. In a previously published study [16], patients with BMI over 30 and lower than 18 were excluded from the study because there is no safe correlation between the pleural surface and the weight of the patient by overweight individuals. The authors suggested that subtracting 20 kg from an overweight patient could normalize the formula; however, this assumption cannot be applied horizontally.

Daily drainage (mL) = 5 x body weight (kg**)** is a new threshold recommendation for chest drain removal. This weight-based formula is physiological and has no demonstrable disadvantage regarding postoperative complications.

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TABLES

Table 1. Demographic and operative characteristics of the patients

	TREATMENT	CONTROL	P-VALUE	OR (95% CI)
SAMPLE SIZE	158	150		
DEMOGRAPHIC CHARACTERISTICS				
AGE (YEARS)	67.1 (10.6)	67.4(9)	0.7928	
WEIGHT (KG)	75.2(16.9)	74.5(14.4)	0.939	
GENDER (M)	82 (%)	76 (%)	0.9325	
OPERATIVE CHARACTERISTICS				
MINIMALLY INVASIVE	145 (91.8 %)	133 (88.7 %)	0.3582	1.43 (0.67-3.05)
LOBECTOMY	74 (46.8 %)	76 (50.7 %)	0.5042	0.86 (0.55 - 1.34)
SEGMENTECTOMY	84 (53.2 %)	74 (49.3 %)	0.50134	1.17 (0.76-1.82)
VATS SEGMENT	83 (52.5 %)	74 (49.3 %)	0.5746	1.14 (0.73-1.78)
VATS LOBE	62 (39.2 %)	59 (39.3 %)	0.9867	0.996 (0.63-1.57)

Mean values of key characteristics of patients in the two groups. The values in parentheses next to the mean values are standard deviations (numerical variables) and percentages (count data). P-values are obtained by t-tests (numerical variables) and chi-squared test (count data). Odds ratios (Wald method) with 95% confidence intervals.

Table 2. Complications - Primary endpoints

	TREATMENT	CONTROL	P-VALUE	OR (95% CI)
SAMPLE SIZE	158	150		
PLEURAL EFFUSION	6 (3.8 %)	7 (4.7 %)	0.7045	0.81 (0.26-2.46)
THORACOCENTESIS/PIGTAIL/CHEST TUBE FOR PLEURAL EFFUSION	3 (1.9 %)	5 (3.3 %)	0.4288	0.56 (0.13-2.39)
DYSPNEA AT FOLLOW UP	20 (12.7 %)	19 (12.7 %)	0.9982	0.99 (0.51-1.96)
WORSE DYSPNEA AT FOLLOW UP	4 (2.5 %)	5 (3.3 %)	0.6762	0.75 (0.20-2.86)
PLEURAL EFFUSION AT FOLLOW UP	2 (1.3 %)	1 (0.7 %)	0.5925	1.91 (0.17-21.3)

The values in parentheses are percentages. P-values are obtained by chi-squared test. Odds ratios (Wald method) with 95% confidence intervals.

Table 3. Complications - secondary endpoints

	TREATMENT	CONTROL	P-VALUE	OR (95% CI)
SAMPLE SIZE	158	150		
PROLONGED AIR LEAK	6 (3.8 %)	2 (1.3 %)	0.1742	2.92 (0.58- 14.70)
CHEST TUBE FOR PNEUMOTHORAX OR EMPHYSEMA	5 (3.2 %)	5 (3.3 %)	0.9334	0.95 (0.27 -3.34)
PNEUMONIA DURING HOSPITAL STAY	4 (2.5 %)	0 (0 %)	0.1448	-
PNEUMONIA AFTER DISCHARGE	2 (1.3 %)	2 (1.3 %)	0.9582	0.95 (0.13- 6.82)
OTHER COMPLICATIONS DURING HOSPITAL STAY	25 (15.8 %)	22 (14.7 %)	0.7779	1.09 (0.59- 2.04)
OTHER COMPLICATIONS AFTER DISCHARGE	4 (2.5%)	0 (0 %)	0.1448	-

The values in parentheses are percentages. P-values are obtained by chi-squared test. Odds ratios (Wald method) with 95% confidence intervals

Table 4. Odds ratios (Wald method) with 95% confidence intervals after removing individuals from the experimental group with drainage < 200 ml/24h at time of removal.

	OR	95% CI	P-VALUE
PLEURAL EFFUSION	0.9802721	(0.4470852, 2.149329)	0.9603266
DYSPNEA	0.5554446	(0.1750453, 1.762507)	0.3123828
COMPLICATIONS	0.5554446	(0.1750453, 1.762507)	0.8769939

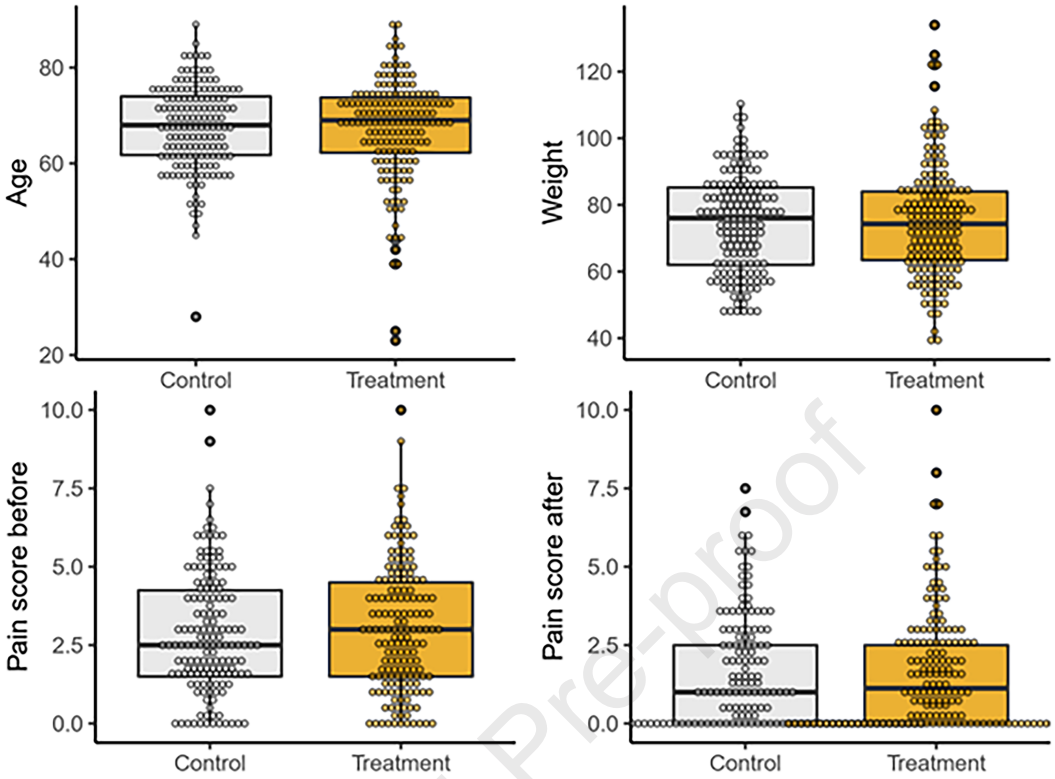
P-values are obtained with χ^2-tests

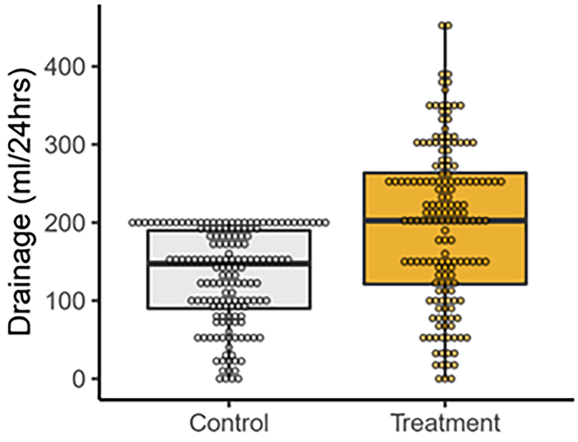
FIGURES

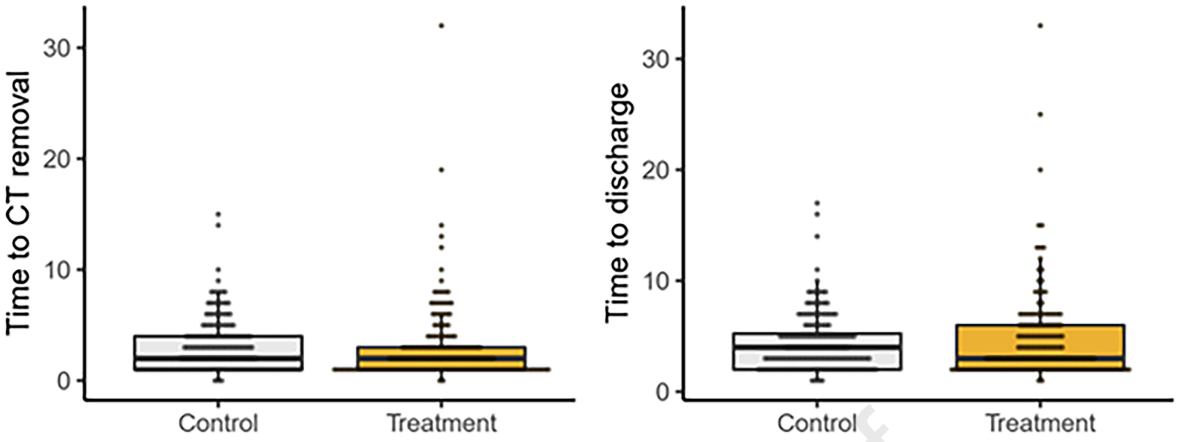
Figure 1. Comparison of key characteristics between groups.

Figure 2. Amount of fluid drained, over the last 24 hours, at the time of chest tube removal.

Figure 3. Time (in days) to chest tube removal and discharge from the hospital.







Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: