

# Outcomes of patients discharged home with a chest tube after lung resection: a multicentre cohort study

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**Background:** Prolonged air leaks are increasingly treated in the outpatient setting, with patients discharged with chest tubes in place. We evaluated the incidence and risk factors associated with readmission, empyema development and further interventions in this patient population.

**Methods:** We undertook a retrospective cohort analysis of all patients from 4 tertiary academic centres (January 2014 to December 2017) who were discharged home with a chest tube after lung resection for a postoperative air leak lasting more than 5 days. We analyzed demographics, patient factors, surgical details, hospital readmission, reintervention, antibiotics at discharge, empyema and death.

**Results:** Overall, 253 of 2794 patients were analyzed (9.0% of all resections), including 30 of 759 from centre 1 (4.0%), 67 of 857 from centre 2 (7.8%), 9 of 247 from centre 3 (3.6%) and 147 of 931 from centre 4 (15.8%) ( $p < 0.001$ ). Our cohort consisted of 56.5% men, and had a median age of 69 (range 19–88) years. Despite similar initial lengths of stay ( $p = 0.588$ ), 49 patients (19.4%) were readmitted (21%, 0%, 23% and 11% from centres 1 to 4, respectively,  $p = 0.029$ ), with 18 (36.7%) developing empyema, 11 (22.4%) requiring surgery and 3 (6.1%) dying. Only chest tube duration was a significant predictor of readmission ( $p < 0.001$ ) and empyema development ( $p = 0.003$ ), with a nearly threefold increased odds of developing empyema when the chest tube remained in situ for more than 20 days.

**Conclusion:** Discharge with chest tube after lung resection is associated with serious adverse events. Given the high risk of empyema development, removal of chest tubes should be considered, when appropriate, within 20 days of surgery. Our data suggest a potential need for proactive postdischarge outpatient management programs to diminish risk of morbidity and death.

**Contexte :** De plus en plus, les fuites aériennes prolongées sont traitées en contexte ambulatoire, le patient retournant à la maison avec un drain thoracique en place. Nous avons évalué l'incidence et les facteurs de risque associés à la réadmission, au développement d'un empyème et aux interventions ultérieures dans une population de patients de ce type.

**Méthodes :** Nous avons mené une analyse de cohorte rétrospective de tous les patients rattachés à 4 centres universitaires tertiaires (de janvier 2014 à décembre 2017) qui, après une fuite aérienne de plus de 5 jours suivant une résection pulmonaire, sont retournés à la maison avec un drain thoracique. Nous avons examinés les paramètres suivants : données démographiques, facteurs liés au patient, détails chirurgicaux, réadmission à l'hôpital, réintervention, antibiotiques prescrits lors du congé, empyème et décès.

**Résultats :** Au total, nous avons analysé 253 patients sur 2794 (9,0 % de toutes les résections), dont 30 des 759 patients du centre 1 (4,0 %), 67 des 857 patients du centre 2 (7,8 %), 9 des 247 patients du centre 3 (3,6 %) et 147 des 931 patients du centre 4 (15,8 %) ( $p < 0,001$ ). La cohorte étudiée comprenait 56,5 % d'hommes, et l'âge médian était de 69 ans (fourchette de 19 à 88 ans). Malgré des durées de séjour initial similaires ( $p = 0,588$ ), 49 patients (19,4 %) ont été réadmis (respectivement 21 %, 0 %, 23 % et 11 % pour les centres 1 à 4,  $p = 0,029$ ), 18 (36,7 %) ont développé un empyème, 11 (22,4 %) ont dû subir une intervention chirurgicale et 3 (6,1 %) sont décédés. Seule la durée d'utilisation du drain thoracique était un prédicteur significatif de réadmission ( $p < 0,001$ ) et de développement d'un empyème ( $p = 0,003$ ), le risque de développer ce trouble étant presque multiplié par 3 avec drain en place pendant plus de 20 jours.

**Conclusion :** L'utilisation d'un drain thoracique pour des patients qui obtiennent leur congé après une résection pulmonaire est associée à des effets indésirables graves. Compte tenu du risque élevé de développement d'un empyème, le retrait du drain devrait être envisagé, lorsque cela convient, dans les 20 jours suivant la chirurgie. Nos données montrent un besoin potentiel en matière de programmes proactifs de gestion des patients externes afin de diminuer le risque de morbidité et de décès.

**P**rolonged air leak (PAL), defined as an air leak lasting longer than 5 days after surgery, is one of the most common postoperative complications after lung surgery, with about 15% of patients who have undergone pulmonary resections remaining hospitalized because of an alveolar air leak.<sup>1</sup> It is potentially associated with a protracted hospital stay and other postoperative complications, such as pneumonia, empyema, atelectasis and need for more interventions, such as thoracentesis or additional chest tube insertion.<sup>2</sup> The current standard practice in most hospitals is to keep patients in the hospital until removal of the chest tube, largely because of surgeon discomfort and lack of high-level evidence and resources regarding outpatient chest tube management. This delay in chest tube removal in patients otherwise ready for discharge can potentially lead to the development of additional complications, and is likely to increase hospital length of stay, which, in turn, is associated with substantial health care costs. For those patients who require a chest tube for treatment of PAL, the length of stay is reported to be increased by about 7.9 days.<sup>3</sup>

However, in an era where health systems are focusing on quality improvement metrics and containment of health care costs, there is an ever-increasing demand for early discharge. Therefore, more surgeons are increasingly sending patients home with in situ chest tubes connected to 1-way valve mechanisms.<sup>4-6</sup>

The development of an outpatient setting for the management of PAL appears to be cost-effective and well appreciated by patients. There are some concerns that outpatient management is not risk-free, and some evidence in the literature suggests increased rates of empyema and readmission associated with prolonged chest tube duration.<sup>7,8</sup> The aim of this study was to evaluate the contemporary rates of postdischarge readmissions within 30 days of discharge before chest tube removal in outpatient or clinic settings, as well as other adverse outcomes among patients discharged home with a chest tube for a PAL after pulmonary resection for primary or secondary malignancies. Our hypothesis, defined a priori, was that outpatient management of a PAL is safe for patients who otherwise meet traditional discharge criteria.

## METHODS

### *Study design and setting*

In this retrospective cohort study design, we collected data from January 2014 to December 2017 from 4 international tertiary academic centres for thoracic surgery at St. Joseph's Healthcare Hamilton, McMaster University (Hamilton, Ontario, Canada), St. James's University Hospital (Leeds, United Kingdom), University College London (London, UK) and Ospedale Maggiore Carlo Alberto Pizzardi di Bologna (Bologna, Italy). Each centre

accessed their local, prospectively collected, institutional surgical databases to extract the data, with supplementary retrospective chart reviews of patient medical records undertaken to complete missing data.

A sample of all patients who underwent a lung resection via either thoracotomy or minimally invasive approaches (video-assisted thoracoscopic surgery [VATS] or robotic resections) was identified in the databases and screened for inclusion criteria. We included patients if their resections were for primary or metastatic lung malignancies, if they had a PAL lasting longer than 5 days and if they were discharged home with a chest tube in place to manage the PAL. A digital electronic device was used in all the patients with suction for the first 24 hours after surgery and after that, if an air leak was present, the suction was removed. On discharge day, the chest tube was connected to a 1-way Heimlich valve. Patients were excluded if they had a postoperative complication other than PAL that resulted in a prolonged hospital stay, if they underwent chemical pleurodesis or if the surgery was for pathologically confirmed benign disease. The exclusion criteria were purposely general to enhance external generalizability and validity of the findings.

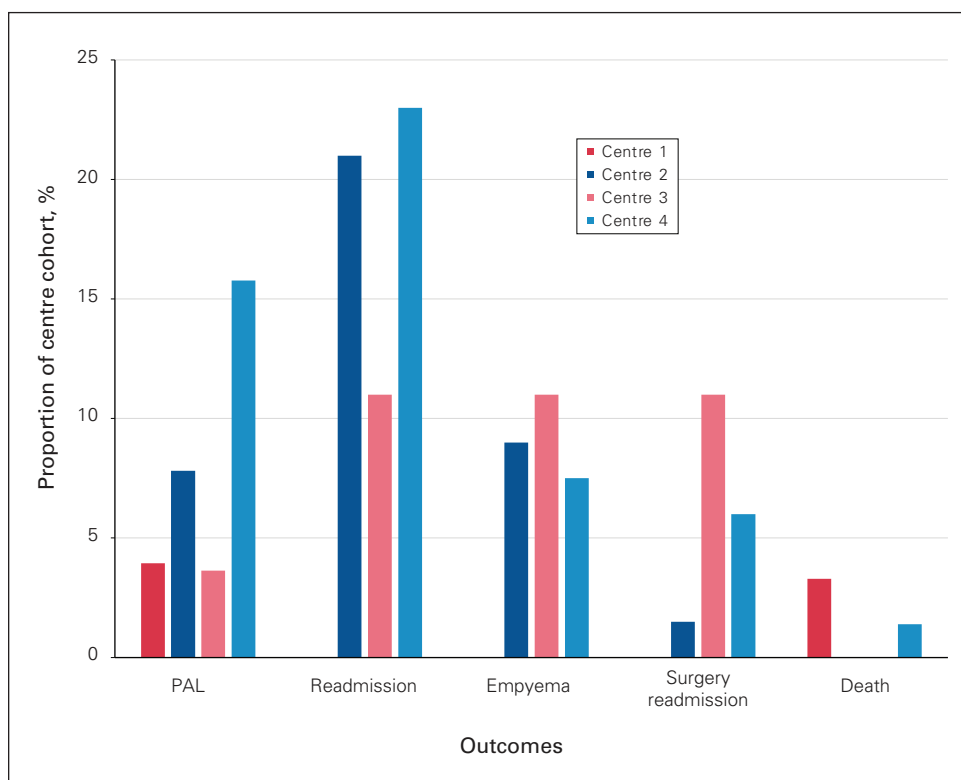
### *Follow-up*

Patients were followed at each centre according to local practice, which included clinic visits every 3–7 days and assessment by thoracic nurse specialists in 2 centres, a weekly visit and assessment by thoracic surgeons in 1 centre and an outpatient postdischarge home care system, overseen by a thoracic nurse navigator (with input from a thoracic surgeon, as needed), in 1 centre.

In all centres, the chest tube was removed when an air leak was no longer detected.

### *Outcomes*

The primary outcome was rate of hospital readmission for any indication within 30 days of discharge from the index surgery with the chest tube remaining in place, as noted in the surgical database or by chart review. Secondary outcomes included the geographic distribution of PAL incidence and adverse outcomes across centres, including the following: hospital readmission because of the development of empyema, defined as fever or leukocytosis associated with computed tomography evidence of pleural fluid infection that required intervention of any kind while the chest tube was still in place for PAL management; hospital readmission because of a need for subsequent surgery for any indication after the index hospitalization timeframe while the chest tube was in place; and predictors of empyema development requiring readmission, a need for postdischarge surgery and 30-day mortality rate.



**Fig. 1.** Proportion of outcomes in the cohort sample, including incidence of prolonged air leak (PAL), hospital readmission, empyema, readmission for surgery and death, showing variance between surgical centres.

### Statistical analysis

We collected data on patient age, sex, approach and degree of resection, forced expiratory volume in 1 second (FEV1), diffusion lung capacity for carbon monoxide (DLCO) measurements from preoperative pulmonary function testing, discharge with antibiotics for any indication, total length of stay and number of days chest tube remained in situ, in addition to outcome measures. We reported continuous variables as means and ranges in normally distributed data; discrete variables were reported as numbers and percentages. We conducted univariable analysis by way of  $\chi^2$  and Mann–Whitney  $U$  tests to assess for patient and operative parameters associated with outcomes postdischarge. We had planned to use logistic regression a priori to evaluate factors associated with risk of empyema development and need for readmission and intervention, but did not perform this given the results of the univariable analysis. We undertook locally weighted scatterplot smoothing (LOWESS) nonparametric local polynomial regression posthoc to assess the relation between chest tube duration and probability of postdischarge empyema development. All tests were 2-sided, and a  $p$  value of 0.05 was considered for statistical significance. All data were deidentified with a sequentially generated study identification code, encrypted and transferred

to the central Hamilton site for analysis. We used STATA version 14 and SPSS version 25.0 for statistical analysis.

### Ethics approval

The study was approved by the Hamilton Integrated Research Ethics Board, project #2018- 4764-C at St. Joseph's Healthcare Hamilton, Ontario, Canada. A waiver of consent was obtained from the remaining centres' institutional review board given the retrospective nature of the review and its minimal risk.

### RESULTS

From January 2014 to December 2017, 2794 patients underwent a lung resection for malignant indications at the 4 institutions; 759 in centre 1, 857 in centre 2, 247 in centre 3 and 931 in centre 4. Of these, 253 (9.0%) were discharged with a PAL and an in situ chest tube (ranging in size between a 20 French and 24 French) connected to a 1-way Heimlich valve, and therefore met the inclusion criteria. The distribution of cases was significantly different among surgical locations ( $p < 0.001$ ), with 9 (4.0%), 67 (7.8%), 9 (3.6%) and 147 (15.8%) surgical cases noted to be discharged with PAL in centre 1, centre 2, centre 3 and centre 4, respectively (Figure 1). Patient and surgery

**Table 1. Characteristics of patients with prolonged air leak discharged with chest tube**

Characteristic	No. (%) of patients*				<i>p</i> value
	Centre 1 <i>n</i> = 30	Centre 2 <i>n</i> = 67	Centre 3 <i>n</i> = 9	Centre 4 <i>n</i> = 147	
Sex					0.180
Male	18 (60.0)	34 (51.0)	8 (89.0)	83 (56.5)	
Female	12 (40.0)	33 (49.0)	1 (11.0)	64 (43.5)	
Age, yr, median (range)	67.5 (48-83)	69 (29-88)	71 (59-79)	70 (19-84)	0.734
Resection					< 0.001
Wedge	2 (6.7)	0 (0)	0 (0)	0 (0)	
Multiple wedges	5 (16.7)	0 (0)	0 (0)	0	
Segmentectomy	0 (0)	13 (19.4)	0 (0)	8 (5.4)	
Lobectomy	21 (70.0)	51 (76.0)	9 (100.0)	135 (92.0)	
Bilobectomy	2 (6.7)	3 (4.5)	0 (0)	4 (2.6)	
Approach					< 0.001
VATS	10 (33.3)	23 (34.3)	9 (100.0)	112 (76.2)	
Open	20 (66.7)	29 (43.3)	0 (0)	31 (21.1)	
Robotic	0 (0)	15 (22.2)	0 (0)	4 (2.7)	
FEV1, median (range)	75 (35-107)	78 (41-137)	90 (75-138)	82 (31-140)	0.047
DLCO, median (range)	73.5 (35-107)	68 (33-112)	87.5 (60-117)	66 (24-998)	0.345
Discharge with antibiotics					< 0.001
No	14 (46.7)	67 (100)	9 (100)	111 (75.5)	
Yes	16 (53.3)	0 (0)	0 (0)	36 (24.5)	
LOS, median (range)	9 (5-14)	8 (4-21)	12 (3-26)	6 (3-63)	0.003
Days with chest tube, median (range)	16 (12-22)	18 (7-66)	17 (7-36)	19 (5-148)	0.120

DLCO = diffusion lung capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 second; LOS = length of stay; VATS = video-assisted thoracic surgery.  
\*Unless indicated otherwise.

characteristics are summarized in Table 1. Overall, the median age of the study cohort was 69 (range 19–88) years, and included 143 (56.5%) men, with no significant difference among centres. Measurements of DLCO were not significantly different among centres ( $p = 0.345$ ), and FEV1 was found to be significantly different ( $p = 0.047$ ). The sites significantly differed on the type of surgery performed and approach of surgery ( $p < 0.001$ ). Overall, pulmonary resection was performed via a thoracotomy in 80 (31.6%) patients and using a minimally invasive (robotic or VATS) approach in 173 (68.4%) patients. Lobectomies represented more than 70% of resections in each centre. The median length of stay associated with the original hospitalization was significantly different among centres 1 through 4, at 9, 8, 12 and 6 days, respectively ( $p = 0.003$ ), but overall chest tube duration was similar at 16, 18, 17 and 19 days ( $p = 0.120$ ), respectively (Table 1).

Home health care was offered to each patient before discharge from the hospital. Prophylactic antibiotic therapy after discharge was prescribed at the discretion of the operating surgeon. In 2 centres, some of the patients discharged home with a chest tube received prophylactic antibiotic therapy after discharge, whereas in the other 2 centres, no patients were discharged on antibiotics, resulting in a significant difference in postdischarge prophylactic antibiotic usage ( $p < 0.001$ ).

### Readmissions

Overall, 49 patients (19.4%) were readmitted for any cause within 30 days of discharge (Table 2), with significant differences observed among centres ( $p = 0.029$ ). There were no differences in the risk between patients who were readmitted on age ( $p = 0.500$ ) or sex ( $p = 0.749$ ), preoperative pulmonary function testing (DLCO  $p = 0.108$ , FEV1  $p = 0.920$ ), resection type ( $p = 0.577$ ) and approach (minimally invasive v. open  $p = 0.750$ ), use of discharge antibiotics ( $p = 0.324$ ), and index length of stay (0.588), with patients differing only on the number of days the chest tubes remained in situ (22 d v. 16 days,  $p < 0.001$ ). Patients who were readmitted for any cause had a significantly different length of stay at readmission across the sites ( $p = 0.016$ ) with an overall median of 0 days and a range of 0–79 days. A length of stay of 0 days represented patients who had their chest tubes removed at the day of readmission.

The most notable causes for readmission within 30 days were empyema with a need for subsequent surgery. Patients who were readmitted and required surgery did not differ by centre ( $p = 0.189$ ), sex ( $p = 0.358$ ), age ( $p = 0.604$ ), resection type ( $p = 0.941$ ), approach ( $p = 0.549$ ), use of discharge antibiotics ( $p = 1.000$ ) or DLCO and FEV1 measurements, but patients with a longer index hospital stay

**Table 2. Characteristics of patients with prolonged air leak discharged with chest tube by readmission status**

Characteristic	No. (%) of patients*		p value
	Readmitted n = 49	Not readmitted n = 204	
Centre			0.029
1	0 (0.0)	30 (14.5)	
2	14 (28.5)	53 (26.0)	
3	1 (2.0)	8 (4.0)	
4	34 (69.5)	113 (55.5)	
Sex			0.749
Male	29 (59.0)	114 (56.0)	
Female	20 (41.0)	90 (44.0)	
Resection			0.577
Wedge	0 (0.0)	5 (2.5)	
Multiple wedges	0 (0.0)	2 (1.0)	
Segmentectomy	6 (12.2)	15 (7.4)	
Lobectomy	41 (83.7)	175 (85.7)	
Bilobectomy	2 (4.1)	7 (3.4)	
Approach			0.959
VATS	29 (59.2)	125 (61.0)	
Open	16 (32.6)	64 (31.5)	
Robotic	4 (8.2)	15 (7.5)	
Discharge with antibiotics			0.324
No	42 (85.5)	159 (78.0)	
Yes	7 (14.5)	45 (22.0)	
Age, yr, median (range)	68 (50 – 84)	70 (19 – 88)	0.500
FEV1, median (range)	80 (32 – 139)	80 (31 – 140)	0.920
DLCO, median (range)	62 (35 – 114)	69 (24 – 998)	0.108
Pre-readmission LOS (range)	8 (3 – 63)	7 (3 – 30)	0.588
Days with chest tube (range)	22 (5 – 141)	16 (5 – 148)	< 0.001
DLCO = diffusion lung capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 second; LOS = length of stay; VATS = video-assisted thoracic surgery.			
*Unless indicated otherwise.			

(10 d v. 7 days,  $p = 0.008$ ) and longer duration of chest tube placement (50 v. 16.5 days,  $p = 0.016$ ) appeared to be at a higher risk of rehospitalization as a result of surgery. Given the small numbers involved, however, these observations are likely unstable. None of the patients included in our analysis had dislodgement of their drains with consequent replacement of chest tube.

Three patients (1 in centre 1 and 2 in centre 4) who were originally sent home with a chest tube in situ died (at 21, 25 and 14 days postoperatively, respectively). Two of the deaths were attributed to empyema and the other was for reasons other than empyema. There were no significant factors other than type of resection ( $p = 0.004$ ) that differentiated between the patients who died and survivors, including the duration of chest tube placement (21 v. 17 days,  $p = 0.736$ ) and index length of stay (8 v. 7 days,  $p = 0.583$ ).

### Development of empyema

Of the 18 patients readmitted as a result of an empyema diagnosis, 11 (61.1%) required a surgical decortication

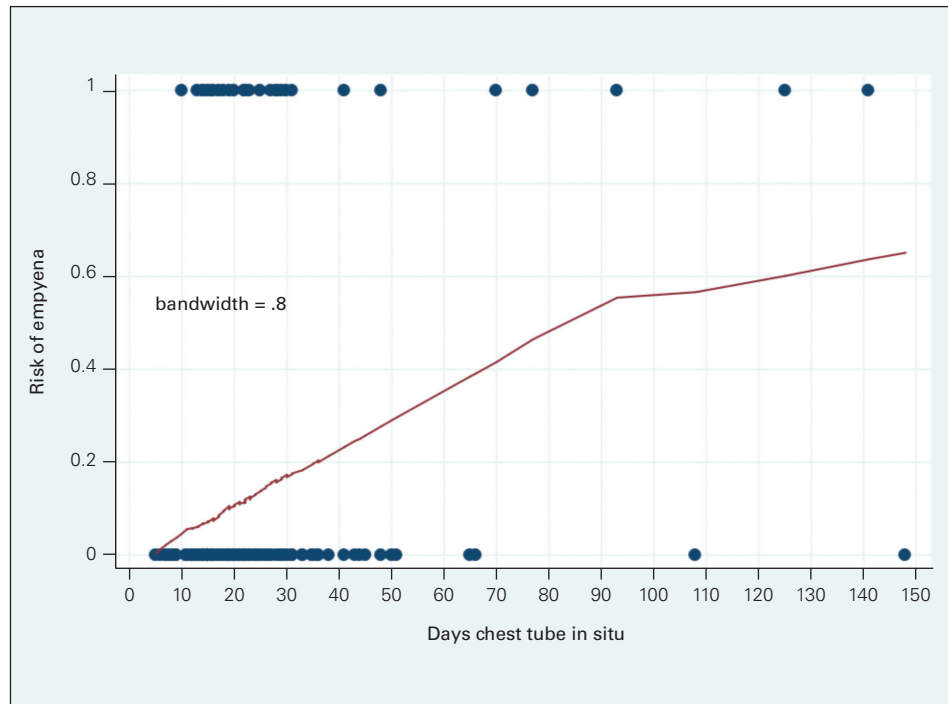
(8 open, 3 VATS), 3 (16.6%) required insertion of an additional chest drain and 4 (22.2%) received antibiotics only, with some patients receiving multiple antibiotic treatments. In terms of patient or surgical risk factors associated with a risk of developing empyema, only the number of days the chest tubes remained in place was a predictor of empyema development (25 v. 16 days,  $p = 0.003$ ). Patients who were readmitted with empyema did not differ by centre ( $p = 0.409$ ), sex ( $p = 0.219$ ), age ( $p = 0.626$ ), resection type ( $p = 0.918$ ) or approach ( $p = 0.310$ ), use of discharge antibiotics ( $p = 0.381$ ), DLCO ( $p = 0.399$ ), FEV1 ( $p = 0.442$ ) or duration of index hospital stay ( $p = 0.198$ ). Upon further analysis, the odds of developing empyema was nearly threefold higher (odds ratio 2.94, 95% confidence interval 1.32–6.54) when the chest tube was left in situ for more than 20 days (Figure 2).

### DISCUSSION

Our analysis included 253 patients discharged with chest tubes because of PAL after lung resections in 4 institutions. The overall readmission rate was 19.4% ( $n = 49$ ) and, of those, 37% ( $n = 18$ ) developed an empyema. We had hypothesized that the empyema rate in patients discharged with chest tubes would be lower than that observed. Most patients (61%) readmitted with empyema required surgery. Moreover, a substantial proportion needed additional drain insertions or antibiotic treatments, and 3 patients eventually died. Hence, the risks of morbidities and death associated with discharging patients home with a chest tube were, in our experience, not negligible. The overall number of days with the chest tube in place was not correlated with increased mortality rates, but it was the only risk factor associated with the development of empyema.

Prolonged air leak after lung resections represents a common postoperative complication. The frequency of patients being discharged home with chest tubes in place to manage PALs is a common concern that is likely to increase over time. With the use of more minimally invasive resections and earlier hospital discharges in the context of Enhanced Recovery After Surgery protocols,<sup>9,10</sup> more patients are expected to be discharged home with a chest tube. The recent adoption of digital drainage systems has allowed clinicians and researchers to better quantify the extent of this problem, which, at minimum, may increase the apparent incidence of these events. In several centres, a common practice for patients with PAL is to pull back the chest tube 1–2 cm every week to try to reduce the air leak duration, especially if the tube's tip is close to the air leak site, thus preventing fusion of the visceral and parietal pleura.

As well described in a review, PAL by itself represents a postoperative complication, delaying hospital discharge



**Fig. 2:** Risk of empyema development over time for patients with in situ chest tube. The locally weighted scatterplot smoothing (LOWESS) plot shows the time-to-event increase of empyema development relative to the time of in situ chest tube. Blue dots represent patients who developed empyema. The risk of empyema (red line) is 20% at 35 days and 50% at 80 days. After 100 days, the risk of clinical empyema plateaus at 60%.

and affecting the quality of care delivered.<sup>11</sup> A single-centre retrospective analysis reported an increased rate of empyema in hospitalized patients with PAL (8%–10%), even if they received oral antibiotics until the air leak stopped.<sup>7</sup> A more recent study showed a statistically significant difference in empyema rates between patients with postoperative PAL and those without (4.8% v. 0.3%,  $p < 0.001$ ).<sup>12</sup> The inpatient setting of these mentioned studies did not seem to positively influence the empyema rate compared with the outpatient setting.

Two previous studies have evaluated outcomes associated with outpatient chest tube management. Between May 2003 and December 2004, Rieger and colleagues discharged 36 patients with PAL with in situ chest tubes, along with digital mini Atrium devices, after lung surgery and reported that 89% of patients had uneventful and successful outpatient chest tube management.<sup>13</sup> A single-centre retrospective analysis from the Mayo Clinic showed that patients discharged with chest tubes in place had a readmission rate of 26.3%, with empyema occurring in 40 of 236 patients (16.9%), representing 4% of their surgeries during the analyzed period.<sup>7</sup> This analysis showed results similar to our study, but used a cohort of patients who underwent surgery between 2004 and 2013, a decade before our study period. Additionally, this study's population included patients who underwent procedures other than lung resection for malignancy (e.g.,

lung transplantation, lung volume reduction surgery, apical bullectomy, pleural decortication), representing a more heterogeneous group. In this study, there were no robotic resections and the rate of VATS procedures increased from 34% to 48% during the decade analyzed,<sup>7</sup> whereas in our study, 68.4% of surgeries were performed via a VATS or robotic approach, representing a more homogeneous, contemporary, multicentre representation of current practice.

### Limitations

Our study presents certain limitations, such as the retrospective design of the study, a large variability of patient characteristics in the patient population, diversity in practice between centres and countries, as well as surgeon preferences in the management of air leaks. This study relied on databases and chart reviews of data originally collected for clinical or quality improvement purposes, and we were limited by the data available. The variability of patient characteristics and clinical practices is a reflection of the multicentred design, and is both a limitation and a strength to the study design. Whereas the external validity of the findings is likely stronger because of a broader sample, the variability in the sample may be obscuring the signal. For instance, it is not clear whether the use of antibiotics helps prevent the development of

empyema. In our study, the use of antibiotics was not systematic, so we cannot provide any clarification about the use of antibiotics. The study could also be criticized for the relatively high proportion of patients discharged home with a chest tube (7.8%), as well as a relatively high rate of readmission (19.4%). We also did not have a unified policy for following and treating those patients after being discharged home, and every centre relied on their own practice pathways. However, we believe that the inclusion of only lung resections for malignancies in our analysis, as well as the inclusion of 4 international centres does provide an adequate assessment of the risks associated with a PALs and outpatient discharge with chest tubes for this specific patient population.

Overall, the inclusion of a contemporary international experience, as well as a relatively large proportion of minimally invasive resections (68.4%), offers updated and representative data for the thoracic surgery literature on this subject.

## CONCLUSION

Home discharge with a chest tube after lung resection, though potentially associated with a shorter length of stay, is also associated with significant adverse events. Given the high risk of empyema development, active prophylactic measures such as pulling back the chest tube 1–2 cm every week, prescribing antibiotics on discharge or removing chest tubes should be considered, when appropriate, within 20 days after surgery. Our data suggest a potential need for an active outpatient postdischarge program to further diminish the subsequent risk of morbidity and death, but this will need to be evaluated prospectively in future studies.

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**Competing interests:** Alessandro Brunelli sits on advisory boards with Ethicon, Medtronic and AstraZeneca, and reports speaking honoraria from Medela and BD. No other competing interests were declared.

**Contributors:** Fabrizio Minervini conceived and designed the work. Takuro Miyazaki, Michal Coret and Laura Schneider contributed to data acquisition. Fabrizio Minervini, Wael Hanna, Alessandro Brunelli, Forough Farrokhyar, Luca Bertolaccini, Marco Scarci, Kristen Hughes, Yessica Lopez-Hernandez, John Agzarian, Christian Finley and Yaron Shargall analyzed and interpreted the data. Fabrizio Minervini and Laura Schneider drafted the manuscript. All authors revised it critically for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

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