Review Article

Postoperative pneumonia in the era of minimally-invasive thoracic surgery: a narrative review

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Background and Objective: The last two decades have been marked by a huge revolution in thoracic surgery. The mainstays of this process have been the advent of minimally-invasive approaches, alongside with the implementation fast-track strategies and other quality improvement programs. In this rapidly evolving scenario, occurrence of postoperative pneumonia (POP) after lung resections remains a serious problem, with reported rates varying from 1.5% to 10%. The goal of this study is to review current knowledge and trends in the management of POP in the context of modern era thoracic surgery.

Methods: A literature search was conducted in order to review the best evidences regarding the following scenarios: (I) influence of minimally-invasive approaches on POPs incidence; (II) current practice in antibiotic prophylaxis; and (III) relevance of rehabilitation protocols in the environment of minimally-invasive lung surgery. Specific Boolean queries were set to this purpose.

Key Content and Findings: The majority of studies show that video-assisted thoracic surgery (VATS) approaches are effective at lowering the incidence of POPs and other complications as well, compared to open surgery. However, data interpretation is somewhat affected by the lack of harmonized definition of POPs amongst studies. Furthermore, some studies did not include POPs as a primary endpoint, thus resulting underpowered in this regard. Operative time, technical proficiency with minimally-invasive surgery, and patient selection can also be important confounding factors. Pre- and post-operative rehabilitation may both amplify the benefits of a minimally-invasive approach. On the other hand, current practice in antibiotic prophylaxis is based on studies dating back more than 30 years ago, a fact that reasonably calls for a revision on the light of modern thoracic surgery needs and problems.

Conclusions: POP remains a relevant problem after lung resections. Adoption of VATS approaches should be encouraged by virtue of a protective effect, ideally in the context of a multidisciplinary program. However, preventive strategies should undergo a focused evaluation, with adequately powered clinical trials.

Keywords: Video-assisted thoracic surgery (VATS); lung resection; enhanced-recovery after surgery (ERAS); rehabilitation; postoperative pneumonia (POP)

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Introduction

The first two decades of 21th century have been marked by a huge transformation in the field of thoracic surgery. One of the mainstays of this process has certainly been the advent of minimally-invasive approaches such as video-assisted thoracic surgery (VATS) and robot-assisted thoracic surgery, which are now replacing the traditional open technique in the vast majority of surgical centers worldwide.

As a matter of fact, changes in surgical technique were only a fraction of a wider revolution, which embraced multiple domains including indications, postoperative management, communication, relationship with patients and many other points. The common denominator of this transition is the shift from a self-referential approach to surgery to a more dynamic one, where all the work processes are subjected to an objective evaluation. The final goal of this attitude is a continuous improvement of the quality of care, in the best interest of patients.

Unfortunately, certain clinical issues persist over time in spite of the advances in surgical practice. Postoperative infections and, in particular postoperative pneumonia (POP) are doubtless amongst these, due to their impact on mortality, hospitalization costs and even long term results. In this review, we sought to take the stock of the situation regarding management of POP in the age of minimally-invasive lung resections, with a view to currently available strategies as well as chances for future implementations. We present this article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-23-20/rc).

Methods

A literature search was conducted on commonly used online libraries (PubMed, Scopus, Google Scholar). Basic Boolean query to browse for publications was set as follows: [(VATS) OR (Videothoracoscopy)] AND [(lobectomy) OR (lung resection)] AND [(postoperative pneumonia) OR (postoperative infection)]. Specific keywords relevant to diverse subheads of this review were added as appropriate (for example: "antibiotics", "prophylaxis", "physiotherapy", and others) (*Table 1*). The preliminary search regarding the core topic (e.g., incidence of POPs after minimally-invasive lung surgery) yielded an initial group of 372 studies. Next, in order to avoid the drawbacks of a redundant literature citation, only studies belonging to the categories of randomized controlled trial, as well as matched retrospective studies with more than 70 patients per group were selected by default. Reviews, observational studies and comparative studies including <70 patients per group were considered if published in journals with at least a Q3 quality mark, according to the SCimago ranking (available at https://www.scimagojr.com). Papers belonging to the category of letter, commentary and editorials were not considered for this review. No strict limits in terms of language and year of publication was adopted, even though priority was given to more recent (<10 years) papers.

Main results

Impact of minimally-invasive approaches on POP

According to US Centers for Disease Control recommendations, POP should defined as the presence of new or progressive radiological findings (infiltrates, cavitation or consolidations), alongside with a combination of various clinical signs including fever >38 ℃, leucopaenia/leukocytosis, altered mental status, sputum changes, respiratory symptoms and worsening gas exchange (1). However, some subtle differences in adopted diagnostic criteria exist amongst centers worldwide. In the setting of postoperative period, most POPs can be considered as hospital-acquired pneumonias, as they usually occur a few days after the admission (or procedure). Much more rarely, POPs can be a consequence of aspiration or ventilator-induced injury. Most relevant causative mechanisms specific to thoracic surgery are impaired chest mechanics, changes in airway microbiota, transient postoperative weakening of immune defenses, and local inflammatory events due to orotracheal intubation, one-lung ventilation and manipulation of the lung.

Since its introduction, it was assumed that VATS would attain a remarkable reduction in postoperative chest infections and other pulmonary complications after major lung resections. The basic assumption is that the minimal traumatism to the chest wall would translate into a reduced pain and preserved muscle contractility, compared to traditional open approach. This would result into more efficient breathing and cough, especially during the early postoperative phase. Furthermore, an attenuated systemic inflammation response was thought to preserve immune function, thereby portending more protection against infections compared to open surgery.

However, POP remains a main problem even in the context of minimally-invasive lung resections. A survey

Table 1 Search summary

Item	Specification
Date of search	7th-10th January, 2023
Databases and other sources searched	PubMed, Scopus, Google Scholar
Search terms used	MeSH: [(VATS) OR (Videothoracoscopy)] AND [(lobectomy) OR (lung resection)] AND [(postoperative pneumonia) OR (postoperative infection)]
	Free terms: Physiotherapy, rehabilitation, uniportal VATS, robotic-assisted thoracic surgery, antibiotics, prophylaxis, enhanced-recovery after surgery
Time frame	No strict limit
Inclusion and exclusion criteria	Inclusion criteria:
	Original studies, either prospective/observational or retrospective
	Systematic reviews/Meta-analyses
	English translation available
	Main exclusion criteria:
	Letters/Editorial/Commentaries
	Small sample size/low journal ranking
Selection process	Independent abstract search (authors 1, 2 and 3)
	Full-text links circulated to all authors
	Ad-interim consensus meeting and literature review (all authors)
	Independent second-look extrapolation of relevant information (authors 1, 2 and 3)
	Final consensus meeting (authors 1, 2 and 3)

VATS, video-assisted thoracic surgery.

from the Beijing General Hospital conducted on over 1,500 patients undergoing curative-intent VATS for lung cancer, the overall incidence of POP was 9.15% (2). Amongst procedure-related factors, longer operative time and intraoperative administration of colloids were significantly related to higher risk. Huang *et al.* reported an impressive readmission rate for POP of 19.8 % after VATS lobectomy in the context of an enhanced recovery after surgery (ERAS) program (3).

Whether VATS approach can still help reduce POPs incidence compared to thoracotomy approach, still remains an open question, especially when comparing prospective studies against retrospective series. Numerous studies, including one meta-analysis (4) showed a clear protective effect of VATS in this regard. However, some other literature data show conflicting results (*Table 2*).

In a recently published double-blinded, multicentric randomized controlled trial conducted in the United Kingdom, VATS lobectomy for early-stage lung cancer led to reduced incidence of in-hospital adverse events, which was mainly due to fewer postoperative infections. On contrary, post-discharge incidence of infections was similar between study groups (5). It should be noted, however, that incidence of postoperative infection was not amongst the primary endpoints of this study. Similar readmission rates due to pulmonary infections were also reported in a large national survey involving 180 hospitals in France (6).

In another single-center trial (7) comparing VATS and open lobectomy, no difference in postoperative morbidity was found. However, even this study did not have postoperative complications as the primary endpoint. Furthermore, only Clavien-Dindo grade 3 and 4 events were included in the analysis, and there is no mention of POP amongst reported complications. This finding might be explained with the fact that no clinically severe pneumonia occurred in either patient group, so that this specific event was not taken into the account of overall postoperative morbidity. Similarly, Long *et al.* (8) did not

Table 2 Most relevant studies regarding POPs occurrence after VATS resections

First author (ref.)	Design/sample size (N)	Country/ region	Year*	Interventions	Key findings	Other
Chen (4)	Meta-analysis (3,457 pts)	–	2013	VATS *vs.* open surgery (subtypes not specified)	Significant risk of POPs after open surgery (5.0% *vs.* 1.6%, P=0.03)	–
Lim (5)	Multicentric RCT (503 pts)	UK	2022	VATS *vs.* open surgery (various subtypes)	Reduced rate of infections in VATS group (16.2% *vs.* 27.8%)	No specific analysis for POPs provided
Bouabdallah (6)	Retrospective, propensity-matched National database (13,207 pts)	France	2021	VATS *vs.* open surgery (various subtypes)	Fewer early infections after VATS (2.8 % *vs.* 4.3%, P<0.001) Similar post-discharge readmissions rate	No specific analysis for POPs provided
Bendixen (7)	Single-center RCT (206 pts)	Denmark	2016	4-port VATS *vs.* anterolateral thoracotomy	No difference in major postoperative complications (24 *vs.* 25 events, P=0.78)	No report of POPs in either group
Long (8)	Multicentric, non-inferiority RCT (425 pts)	China	2018	Multiport VATS (3–4 accesses) *vs.* axillary thoracotomy	No difference in POP incidence (VATS: 1.4%, Open: 2.4%, P=0.966)	POP defined on CURB-65 criteria
Desai (9)	Retrospective, propensity-matched National database (27,451 pts)	USA	2017	VATS *vs.* open (subtypes not specified)	Lower incidence of infections after VATS (1.65% *vs.* 3.31, P<0.001)	POP defined on ICD records
Paul (10)	Retrospective, propensity-matched National database (6,323 pts)	USA	2010	VATS *vs.* open (subtypes not specified)	Quasi-significant reduction of POP after VATS (2.97% *vs.* 4.37%, P=0.075) Cumulative respiratory complications rate lower after VATS (P<0.0001)	Definition of POP not specified
Wang (11)	Retrospective cohort study (1,501 pts)	China	2022	VATS *vs.* open (subtypes not specified)	Open approach was an independent risk factor for POP (OR: 5.5, P<0.0001)	Definition of POP based on CDCP criteria
Agostini (12)	Observational, propensity-matched (524 pts)	UK	2017	VATS *vs.* open (subtypes not specified)	Lesser incidence of POPs after VATS (7.4% *vs.* 18.6%, P<0.001)	Definition of POP based on established criteria
Falcoz (13)	Retrospective, propensity-matched International database (28,771 pts)	Europe	2016	VATS *vs.* open (subtypes not specified)	Same incidence of POP (VATS: 6.0%, Open: 6.2%, P=0.77) Cumulative morbidity lower after VATS (P=0.035)	Definitions of POP and other complications based on established criteria
Pagès (14)	Retrospective, propensity-matched National database (24,881 pts)	France	2016	VATS *vs.* open (subtypes not specified)	VATS marginally associated with lower risk of POP (OR: 0.62, P=0.055) No difference in high-risk patients Risk of hidden bias	Definition of POP not specified

Table 2 (*continued*)

Table 2 (*continued*)

First author (ref.)	Design/sample size (N)	Country/ Region	Year*	Interventions	Key findings	Other
Laursen (15)	Retrospective National database (1,379 pts)	Denmark	2016	VATS *vs.* open (either anterior or posterolateral)	Reduced POPs incidence after VATS (7.5% *vs.* 10.6%, P=0.045)	Definition of POP not specified
Dziedzic (16)	Retrospective, multicentric National database (6,265 pts)	Poland	2021	Multiportal VATS (2 or 3 ports) *vs.* muscle-sparing thoracotomy	Lesser incidence of POPs after VATS (6.7% *vs.* 16.3%, P<0.001)	Definition of POP not specified
Stephens (17)	Retrospective, propensity-matched (963 pts)	USA	2014	Multiportal VATS (2–4 ports) *vs.* muscle-sparing thoracotomy	No difference in POP rate (6% *vs.* 9%, P=0.12)	Definition of POP not specified
Flores (18)	Retrospective, single-center (741 pts)	USA	2009	3-port VATS *vs.* posterolateral thoracotomy	Lesser complications rate after VATS (24% *vs.* 30%, P=0.05) No difference reported in propensity-score extremes	No separate analysis for POP provided
Scott (19)	Secondary analysis from RCT data (964 pts)	USA	2010	VATS *vs.* open (subtypes not specified)	Lesser atelectasis rate after VATS (0% *vs.* 6.3%, P=0.035) Similar incidence of sepsis, empyema, and respiratory failure	No separate analysis for POP provided

*, year of publication (either online or printed version). –, meta-analysis of studies from multiple countries/regions. POP, postoperative pneumonia; VATS, video-assisted thoracic surgery; ref., reference; pts, patients; RCT, randomized controlled trial; OR, odds ratio; CURB-65, confusion, urea, respiratory rate, blood pressure, age >65 years; ICD, international classification of diseases; CDCP, Centers for Disease Control and Prevention.

found any difference in POP between patients undergoing either VATS or open lobectomy. Even in this study, all POPs were classified as mild or moderate, with no patient in either group developing severe pneumonia according to CURB-65 criteria.

In a survey of the Healthcare Cost and Utilization Project database, the incidence of postoperative infection after VATS lobectomy for was halved compared to open approach (1.65% *vs.* 3.31%, P=0.001). This propensity-matched, retrospective study included more than 9,000 patients per group. However, some relevant clinical data were missing and it is unclear as to whether the study groups were similar in terms of pathological staging and baseline degree of respiratory impairment (9). A propensity-matched analysis from the Society of Thoracic Surgeons' database (10) including more than 6,000 patients found that VATS lobectomy resulted into a lower incidence of postoperative pulmonary complications as a whole, and in overall postoperative infections as well. However, difference in POPs incidence did not reach statistical significance. It should that this study included patient cases operated on between 2002 and 2007, thus in a relatively early historical phase of VATS lobectomy.

Wang *et al.* (11) analyzed retrospectively 1,501 patients undergoing different lung resections (mostly, anatomical resections for lung cancer), in order to develop a predictive model for early-onset POP. The most striking result of this study was that, amongst tested variables, VATS approach showed a very strong correlation with a reduced risk. Yet another independent predictor was the degree of postoperative pain, thus suggesting that the benefits of a minimally-invasive approach are mostly driven by improved pain control in the early postoperative period. A remarkably lower incidence of POP after VATS was also retrospectively reported by Agostini and coworkers, who also showed a reduced need for postoperative physiotherapy sessions compared to open surgery (12). In a propensity-matched retrospective analysis of the European Society of Thoracic

Surgeons database, Falcoz reported a significantly reduced incidence of cumulative postoperative morbidity rates after VATS lobectomy compared to open approach (13). However, the rates of POP and pleural empyema were the same. Yet another large propensity-matched analysis from a French database (14) showed a lower rate of pneumonia and a shorter hospital stay after VATS. The Copenhagen group (15) reported that VATS approach resulted in a significantly lower 30-day morbidity rate, with a significantly lesser incidence of POPs and sepsis. This observation was consistent amongst different cancer stages.

A significantly lower incidence of POP was also reported by Dziedzic and coworkers (16) in another large retrospective analysis. Stephens *et al.* reported a remarkably lower incidence of pulmonary morbidity with VATS, even though the number of POPs and other infections were similar compared to a muscle-sparing thoracotomy (17). Flores *et al.* reported a lower overall morbidity in after VATS lobectomy, but the authors did not provide a separate analysis restricted to POP only (18). Furthermore, the difference seemed to disappear in propensity-score extremes. Similarly, a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 showed reduced overall morbidity with VATS lobectomy and lower atelectasis rate, but no difference in terms of POP and pleural empyemas (19).

Benefits of VATS in patients with chronic obstructive pulmonary disease (COPD) and other comorbidities

A low forced-expiratory volume at 1 second (FEV1) status is one of the main risk factors of POPs and other complications after lung resection (20). Therefore, an important question is whether VATS approach can be beneficial when restricting the analysis to patients with COPD of various degrees.

In this regard, only retrospective data are available, although reference studies are generally of good quality with a relatively low risk of bias. The Seoul group showed that, compared to open surgery, VATS lobectomy can achieve a threefold reduction in POP in patients with COPD and stage I non-small cell lung cancer (21). Interestingly, in this series, all deaths due to pneumonia occurred in patients who received open surgery.

In a large survey from the Italian VATS Group, it was shown that in patients with impaired pulmonary function (as indicated by either diffusion-capacity for carbon monoxide or FEV1 <60% predicted, the incidence of POP after VATS lobectomy was 5.4%. Although this rate was significantly higher than patients with normal respiratory function, neither parameter worked as a reliable predictor of POP (22).

A protective effect of VATS in patients with a low FEV1 status was also retrospectively reported by Ceppa *et al.* (23). Other results in line with these observations were excellently summarized by Oparka *et al.* in a Best Evidence Topic published in 2013 (24).

In an elegant study, Donahoe *et al.* compared the results a subgroup of patients classified as high-risk based on pulmonary function tests and other comorbidities. In these patients, adoption of VATS approach was able to abate the frequency of POPs and other complications, so that cumulative postoperative morbidity was similar to patients with a standard risk (25). However, the number of patients who received VATS lobectomy in the high-risk subgroup was low (72 patients *vs.* >500 patients with standard risk), so that study's conclusions should be taken with caution due to a potential for type II error.

Role of robot-assisted thoracic surgery

Compared to standard VATS, robot-assisted thoracic surgery is supposed to offer the further advantage of a more precise dissection, thus contributing to an overall reduction of surgical traumatism. Whether this fact has as a positive impact on postoperative outcomes it is still a matter of debate. Interestingly, however, a significant reduction of POPs incidence (7.2% *vs.* 21.6%, P<0.05) has been reported in a propensity-matched study by Pan *et al.* (26). Similarly, in a large national survey, Alwatari found a twofold reduction in POPs (1.6% *vs.* 3.5%, P<0.01) after robot-assisted sublobar resections compared to standard VATS (27). However, this effect was not seen after lobectomies. One meta-analysis showed a significant reduction of pooled postoperative morbidity rate after robotic-assisted major lung resections compared to VATS, but not specific data on infectious events were analyzed (28).

Role of uniportal VATS

Since its introduction in the early 2010's, uniportal VATS is attracting an increasing number of thoracic surgeons worldwide. The main advantage of uniportal VATS is the use of just a single chest incision, a fact that would translate into reduced surgical pain. Furthermore, as a paradox, the single incision implies that the orientation of surgical instrument is more similar to open surgery, rather than standard VATS. This particular setting results into a reduced stretching of intercostal bundles, a fact that it is

expected to further attenuate postoperative pain. Several studies so far have shown that uniportal VATS is as feasible as standard VATS in many operational instances. A meta-analysis also showed that it may prove advantageous in terms some postoperative outcomes, such as drainage removal time and length of stay (29). However, whether uniportal VATS might help reducing POPs is much less clear. Incidence of POP as a separate event was analyzed in one study only. In this study, no difference was reported compared standard multiport approach, even though cumulative complication rate was lower (30).

Role of locoregional anesthesia (LA) techniques

LA is one of the mainstays of modern-era thoracic surgery. In the ERAS philosophy, use of LA is strongly recommended, with the goal of limiting the undesired side-effects of opioids (31).

Adopted LA techniques may vary in terms of site of administration, used drugs and dosages, and modality of administration (one-shot versus continuous). A thorough comparison of the diverse LA schedules is beyond the scope of the present review. An example of the potential benefit of LA in terms of POPs prevention came from Gao *et al.*, who reported a significant reduction in POP by applying serratus anterior plane block in VATS lobectomy patients (32). Given that other LA techniques such as erector-spinae block or paravertebral block may be effective as well at controlling postoperative pain (33,34), it seems reasonable that a reduction in POPs and other complications might be also attained with these alternative approaches.

To conclude, the overall impression is that, generally speaking, minimally-invasive thoracic approaches have the potential for mitigating the incidence of POP and other respiratory complications, even though certain factors might amplify or attenuate the size of overall benefits in the real-world scenario. These modulating factors might include technical proficiency with VATS and robotic-assisted thoracic surgery technique, operative time, careful patient selection and optimized pre- and postoperative patients' management. These considerations strongly remind that minimally-invasive approaches in major lung resections can achieve optimal results when implemented in a well-established quality improvement program, rather than when performed sporadically.

Not surprisingly, some results also indicate that the benefits of VATS lobectomy in terms of postoperative infections seem to peak in the early postoperative phase, while slightly decreasing over time. Further prospective trials should be planned in order to adequately evaluate the benefits of VATS in specified patients' subgroups, such as those with more advanced COPD, ageing, frailty and other relevant comorbid conditions.

Antibiotic prophylaxis

By definition from the Surgical Wound Infection Task Force, most thoracic procedures are regarded as "clean contaminated" operations, with the major exception being the presence of pleural empyema (35). With this said, it is reasonable to consider antibiotic prophylaxis as an essential step in reducing morbidity and mortality after lung resections. However, the current practice in this regard is founded on clinical studies dating back between the 1970s and the 1990s. At that time, minimally invasive techniques were not widely employed, at least for major lung resections. Furthermore, in a dedicated review, Chang and Krupnick (36) highlighted that the current practice of antibiotic prophylaxis in thoracic surgery is largely founded on studies that were not specifically focused on lung resections, and that did not even include respiratory infections amongst the primary outcomes.

The current practice of antibiotic prophylaxis had then little changed over the past 30 years. Many thoracic surgery centers worldwide still favor the administration of a single dose of cefazolin before incision. Indeed, the use of extended antibiotic prophylaxis has been repeatedly shown useless to decrease the risk of post-operative infections in diverse surgical fields. Interestingly, however, Deguchi *et al.* reported a protective effect of extended intravenous cefazolin until postoperative day 3. This study included more than 400 patients, many of which received VATS lobectomy (37).

Some authors also questioned whether a new antibiotic prophylaxis regimen should be implemented. Schussler *et al.* designed a prospective study comparing cefamandole (3 g/24 h over 48 hours) versus amoxicillin-clavunate (6 g/24 h over 24 hours) (38). They showed a statistically significant decrease in both POPs and other postoperative infections in the second group. The results remained statistically significant after adjusting for type of resection, age, BMI, gender, colonization and presence of COPD. Radu and colleagues retrospectively analyzed 312 cases of major lung resection performed in their center (39). They reported that 24% of patients undergoing major pulmonary resections and treated with standard antibiotic prophylaxis,

ultimately developed POP. In-hospital mortality among them was 26%. In this study, *Enterobacteriaceae*, *S. pneumoniae*, *Haemophilus* spp. and *S. aureus* were the most commonly involved pathogens. According to antibiograms, only 18% of cultured germs were susceptible to cefazolin. Furthermore, Yamada *et al.* showed that, especially in COPD patients, pathogens isolated during postoperative chest infection substantially differed from those isolated on preoperative cultures (40). These results raised the concern that currently adopted antibiotic prophylaxis strategies might be of scant efficacy in preventing POP after lung resections in the modern era surgery, and urgently call for a rethinking.

Finally, the appropriate timing for starting a therapeutic antibiotic treatment is still unclear, even though it is universally recommended that antibiotics are commenced within 1 hour after identifying a frank septic state. However, unmasking early onset of POPs might be an extremely difficult task after lung resection, due to the overlap of suspicious clinical changes that might still not be due to ongoing chest infections (e.g., hypoxia, phlegm discoloration, chest pain, labored breathing pattern, and so on). Inappropriate antibiotic regimen portends a spectrum of detrimental effects, including toxicity, ineffectiveness and selection of resistant strains. Therefore, it is of a paramount importance that therapeutic decisions regarding the timing of treatment and choice of antibiotics are made following a solid rationale. Even though the topic of POPs treatment is beyond the goal of the present review, we found worth of mentioning a Spanish paper from Plata-Menchaca and Ferrer, where a sound decisional algorithm for POPs treatment is proposed (41).

To conclude, new studies are needed to refine current antibiotic prophylaxis guidelines in the field of lung resections. Appropriate antibiotic prophylaxis in the contemporary era should take into account the most common responsible pathogens, and it should also consider the peculiar clinical and physiopathological implications of minimally-invasive approaches, especially in the early postoperative phase.

Preoperative and postoperative rehabilitation

Word Health Organization defines rehabilitation as a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions. The main goals of rehabilitation in thoracic surgery are to optimize breathing mechanics, to improve bronchial cleansing, and to increase exercise tolerance. However, rehabilitation protocols greatly vary in terms of duration, objectives, modality of administration and type of adopted interventions (*Table 3*).

In a sense, rehabilitation and implementation of minimally-invasive thoracic procedures both look at same direction, that is, to preserving and restoring patients' physical efficiency as much as possible. Furthermore, even in absence of formal rehabilitation framework, it is of a paramount importance that the patients are encouraged to early mobilization as soon as possible after the operation (52).

Many studies so far have been highlighting the benefits of perioperative rehabilitative interventions in lung resections in general. In two meta-analyses including 9 and 13 studies respectively, preoperative rehabilitation with breathing exercises and/or inspiratory muscle training has shown a consistent effect on reducing the incidence of pulmonary complications (42,53). Similar results were reported in another pooled analysis focused on prehabilitation training only (43). However, all these meta-analyses did not taken into the account the impact of surgical approach.

On contrary, a relatively lower number of studies so far are available to address the question whether in the field of minimally-invasive lung resections, rehabilitation can still have the same beneficial impact as after open surgery in preventing POPs and other pulmonary complications.

Recently, a large retrospective study of pulmonary rehabilitation in a context of ERAS was published (44). All patients in both groups received VATS lobectomy as well as a comprehensive ERAS management including no fasting, postoperative euvolemia, standardized analgesia regimen, timely chest drain removal, and other interventions. Study group also received both pre- and postoperative rehabilitation which included diaphragmatic breathing exercises, supervised coughing/huffing sessions, and daily aerobic training. Pulmonary rehabilitation attained an impressive reduction in POPs (15% *vs.* 28.3%, P<0.001) compared to patients who received ERAS protocol alone.

A small randomized controlled trial evaluated the benefits of a multimodality rehabilitation program including inspiratory muscle exercises versus breathing exercises alone after major lung resection, in high-risk patients (45). It was shown that the net effect of the intervention did not differ substantially amongst patients received either VATS or open approach. However, the most relevant achievement was improvement of postoperative arterial oxygenation, while the incidence of POPs and other pulmonary complications was not modified by implementation of

Table 3 Most relevant studies regarding POPs after rehabilitation protocols

First author	Design/sample size (N)	Country/ Region	Year*	Interventions	Key findings	Other
Mao (42)	Meta-analysis (2,501 pts)	–	2021	Pre and postoperative (various)	Significant risk-reduction for pulmonary complications (OR: 0.38)	Includes both VATS and open operations
					Very low heterogeneity (I^2: 0%)	
Granger (43)	Meta-analysis (636 pts)	–	2022	Preoperative (various)	Significant risk-reduction for pulmonary complications (OR: 0.45)	–
					Very low heterogeneity (I^2: 0%)	
Zheng (44)	Multicentric RCT (374 pts)	China	2023	Comprehensive pre- and postop rehabilitation *vs.* standard ERAS care	Fewer pulmonary complications in the study group (15% *vs.* 28.3%, P<0.001)	All patients underwent VATS approach
Brocki (45)	Single-center RCT (70 pts)	Denmark	2016	Inspiratory muscle training *vs.* standard breathing exercise	Non-significant trend to lower POPs rate in the experimental group (7% *vs.* 21%, P=0.21)	Definition of POP specified
						All patients with high-risk of POP
						Includes both VATS and open approach
Agostini (46)	Observational (285 pts)	UK	2020	Postop physiotherapy as needed	7% incidence of POP	Definition of POP specified
						All patients received VATS
Agostini (12)	Observational, propensity-matched (524 pts)	UK	2017	VATS + postop physiotherapy as needed	Lesser incidence of POPs in VATS group (7.4% *vs.* 18.6%, P<0.001)	Definition of POP specified
				Open + postop physiotherapy as needed	Fewer patients needed physiotherapy in VATS group (P<0.001)	
Chao (47)	Retrospective, single-center (125 pts)	Taiwan	2022	Tailored pre- and postop rehabilitation protocol according to CPET results	Tailored rehabilitation equalizes postoperative morbidity in patients with different CPET results (P=0.210)	POP definition based on chart review
				All VATS patients		No separate analysis for POP
Liu (48)	Retrospective, National database (7,549 pts)	Taiwan	2019	Incentive spirometry *vs.* standard postop physiotherapy	Incentive spirometry reduces POPs rate after VATS (23% *vs.* 36%, P<0.05)	POP defined on ICD records
				Separate analysis after VATS and open	No effect after open surgery (OR: 0.9)	
Zhou (49)	Single-center RCT (86 pts)	China	2022	Physical manipulation *vs.* standard postop physiotherapy	No effect on POPs incidence (4.5% *vs.* 7.1%, P=0.60)	Definition of POP not specified
				All VATS patients	Shorter hospital stay in the study group	

Table 3 (*continued*)

Table 3 (*continued*)

First author	Design/sample size (N)	Country/ Region	Year*	Interventions	Key findings	Other
Zou (50)	Single-center RCT (90 pts)	China	2022	Multimodal rehabilitation program *vs.* basic postop rehabilitation (nurse led)	Fewer complications in the study group (8.89% *vs.* 33.3%)	Events defined on chart review
				All VATS patients		
Liu (51)	Single-center RCT (73 pts)	China	2020	Multimodal pre-habilitation program *vs.* no pre-habilitation	Same POP incidence (0% *vs.* 1%, P=0.3)	No definition of POPs
				All VATS patients		

*, year of publication (either online or printed version). –, meta-analysis of studies from multiple countries/regions. POP, postoperative pneumonia; pts, patients; RCT, randomized controlled trial; ERAS, enhanced-recovery after surgery; VATS, video-assisted thoracic surgery; CPET, cardio-pulmonary exercise test; OR, odds ratio; ICD, international classification of disease.

inspiratory muscle training.

Agostini *et al.* (46) analyzed a series of 285 patients undergoing VATS lobectomy at a high-volume center. It was found that up to 73% of them presented with events calling for physiotherapy support due to poor mobility and/or development of pulmonary complications as defined by the Melbourne Group Scale. In this study, COPD, age >75 years, obesity and a preoperative 6-minute walk test <400 meters were independently associated with the need of postoperative physiotherapy. On the basis of these results, the authors recommend early physiotherapy consult in all VATS lobectomy patients. However, in a different publication, the same author also showed that, in general, VATS patients required less physiotherapy contacts and generally shorter physiotherapy sessions (12). These observations can be interpreted as the establishment of sort virtuous circle, with a mutual beneficial tradeoff between minimally invasive approaches and rehabilitative interventions.

Chao *et al.* assessed the results of a comprehensive perioperative rehabilitation program in patients who received VATS resections (mostly wedge resections and lobectomies) (47). The program entailed both pre- and postoperative interventions, that included breathing exercises, early ambulation, inspiratory muscle training, and others. Patients were grouped into risk-class according to cardio-pulmonary test parameters, and they were also given a different exercise intensity in keeping with their level of fitness. Interestingly, the authors found that respiratory complications occurred with the same frequency regardless the baseline fitness level. This observation authorize the authors to conclude that a tailored perioperative rehabilitation program should be recommended in all VATS resection patients. It should be noted, however, that in this study there were a very small number of patients in the "high-risk" group, so that results should be interpreted with caution.

Liu *et al.* (48) utilized incentive spirometry in a large retrospective series of patients undergoing either VATS or open lung resection. It was reported that incentive spirometry was used less frequently in VATS patients. Nonetheless, these patients still exhibited a benefit from this intervention in terms of POP and hospitalization costs as well (mean difference: –542.5 USD).

In a small randomized controlled trial, Zhou and Sun (49) showed that implementation of physical manipulation to a standard chest physiotherapy protocol can improve lung function parameters after VATS lobectomy. However, no effect was noted on incidence of POP.

Zou *et al.* randomized 86 VATS resection patients, to receive a postoperative rehabilitation program including positive pressure vibration therapy, cycling, and square dancing. In the intervention group, there was a significant reduction in postoperative complications, mainly driven by lowed incidence of POPs and atelectasis (50).

On contrary, a specifically designed, small randomized-controlled trial showed that a comprehensive, home-based prehabilitation plan failed to reduce overall complication rates after VATS lobectomy, although submaximal exercise capacity as measured by 6-minute walk test was higher after the operation (51).

To conclude, despite some discrepancies between

studies, literature data seem to indicate that—in the setting of minimally-invasive thoracic surgery—perioperative rehabilitation can be effective at further reducing the risk of POPs and other respiratory complications. Again, these benefits seem more consistent if included in multidisciplinary context aimed at favoring patients' involvement with the rehabilitation program. In this scenario—as also highlighted in the dedicated section of this review—adopted tools should also include a widespread usage of locoregional analgesia techniques. For example, Kang *et al.* showed that in the setting of VATS resections paravertebral block facilitates early mobilization and effectiveness of rehabilitative programs (54). Last but not least, the paramount importance of non-clinical interventions such as patients education, motivation and encouragement should be always reminded.

Conclusions

In the era of minimally-invasive thoracic surgery, development of postoperative infections still remains a relevant clinical problem. However, mitigating strategies are possible, provided that they are implemented in a dynamic and proactive environment. For example, adoption of minimally-invasive approaches themselves can contribute to reduce the risk of POPs and other serious complications, but it is essential that technical proficiency is pursued in order to shorten operative times and optimize surgical maneuvering. Without these achievements, there might be a serious risk of dissipating the potential benefits and obtain postoperative outcomes even worse than a traditional open approach. Therefore, it is of a paramount importance that—when developing a VATS program—the postoperative results are subjected to critical discussion and a constructive auditing. The role of alternative minimally-invasive approaches such as uniportal VATS and robot-assisted thoracic surgery is still unclear, with some small studies suggesting a protective effect probably by virtue of reduced surgical traumatism and better pain control. Implementation of rehabilitation programs seems to remain beneficial as a mean to prevent POPs and other complications after minimally invasive lung resections, so that resources should be allocated to this scope. Finally, this literature review highlighted the lack of a harmonized definition of POPs amongst reference studies, thereby adding some uncertainty to data interpretation.

A focused revision of current antibiotics prophylaxis strategies should also be taken into consideration, under the light of modern thoracic surgery needs and problems.

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Footnote

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