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Review article

Persistent cough after pulmonary resection: Minor issue, major hurdle

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ABSTRACT

Background: Persistent cough is one of the most common complications following pulmonary resection, that impairs patients' quality of life and prolongs recovery time. However, a comprehensive review of persistent cough after pulmonary resection (CAP) has not been performed.
Methods: A literature search of PubMed/MEDLINE, Web of Science, and Embase database was conducted for persistent-CAP up to June 2023. Subsequent qualitative systematic review focused on definition, risk factors, prevention, and treatment of persistent-CAP.
Results: Persistent-CAP stands as a prevalent postoperative complication subsequent to pulmonary resection procedures. with an incidence of 24.4–55.0 %. Although persistent-CAP has a minor impact on survival, this condition is of critical importance because it presents a major hurdle in recovery after surgery. In this review, we proposed a systemic definition for persistent-CAP based on available evidence and our own data. Several assessment tools used to assess severity of persistent-CAP are also introduced. Risk factors associated with persistent-CAP are explored, including surgical approaches, resection extent, surgical site, lymph node dissection, postoperative gastroesophageal acid reflux, tracheal intubation anesthesia, preoperative comorbidity, and sex among others. Surgical and anesthesia preventions targeting risk factors to prevent persistent-CAP are elaborated. A number of studies have shown that a multidisciplinary approach can effectively relieve persistent-CAP.
Conclusions: Although the mechanisms underlying persistent-CAP are still unclear, existing studies demonstrated that persistent-CAP is related to surgical and anesthesia factors. Therefore, in the

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future, prevention and treatment should be developed based on risk factors to overcome the hurdle of persistent-CAP.

1. Introduction

Given the extensive application of low-dose CT in the screening of lung neoplasms and the increasing incidence of lung cancer, the number of pulmonary resections is also increasing [1,2]. For more than two decades, the safety, efficacy, and minimal invasiveness of surgery have been the focus of research in the field of pulmonary surgery. Nevertheless, inadequate focus has been directed towards persistent cough after pulmonary resection (CAP), a frequently encountered complication arising from lung surgery., with limited literature on risk factors, prevention, and treatments for persistent-CAP.

Studies investigating CAP demonstrated that approximately 24.4–55.0 % of patients report experiencing cough after pulmonary resection [3–5]. CAP exacerbates postoperative pain, prolongs hospitalization, and undermines patient quality of life (QOL) [6]. Therefore, identifying the risk factors and evaluating prevention and treatment of postoperative cough are of great significance for rapid recovery and improvement of QOL in patients after pulmonary resection [7].

At present, the exact mechanisms causing postoperative persistent cough are still unclear, and there is no consensus on appropriate prevention and treatment. Previous studies have demonstrated that CAP is associated with surgical interventions, anesthesia procedures, and other individual factors [8–10]. The objective of this review was to propose a novel definition of persistent-CAP, summarize the risk factors, prevention, and treatment strategies for persistent-CAP, and provide clues for further research.

2. Material and methods

A comprehensive literature review was conducted covering the PubMed/MEDLINE, Web of Science, and Embase database up to June 2023. The following terms were used: (1) population: lung, pulmonary, pulmonary neoplasm; (2) intervention: surgery, resection, lobectomy, pneumonectomy, segmentectomy, thoracic surgery, video-assisted thoracic surgery; (3) outcome: cough, coughing, persistent cough, chronic cough. We reviewed the reference lists of identified articles for any publications we may have missed in our search. Duplicate entries were eliminated after importing the search records into Endnote X9.

The inclusion criteria were as follows: articles that (1) were full-text original publications in English, (2) presented the measure or characteristics of cough, and (3) targeted patients underwent pulmonary resection. Expert opinions, animal and case studies, conference abstracts, and publications that were not peer-reviewed were excluded.

3. Results

The database search yielded 5429 studies in total, of which 2557 duplicate entries were excluded. A total of 2747 studies were eliminated after screening title and abstract based on the inclusion and exclusion criteria. Subsequently, 109 studies were excluded upon full-text review. Finally, 16 studies regarding cough after pulmonary resection were included (4 randomized controlled trials, 12 cohort studies, and 7 involved retrospective patient cohorts).

4. Definition of persistent cough after pulmonary resection

There is no well-recognized definition for persistent-CAP within current literature or medical guidelines. Sawabata et al. defined CAP as a non-productive cough occurring after surgery in individuals exhibiting stable chest X-ray findings, devoid of postnasal drip syndrome, asthma, or prior utilization of angiotensin-converting enzyme inhibitors (ACEI) [11]. We considered cough duration to be essential, as most short-term or occasional cough requires little intervention, but duration was not defined in this research. Xie et al. [5] proposed that cough symptoms lasting for $\geq$8 weeks constitute a chronic cough, based on the diagnostic criteria of chronic cough established by the American College of Chest Physicians (ACCP) [12]. However, the definition of chronic cough may not conform to that of persistent-CAP as their mechanisms may differ. In an observational study, Sawabata et al. added that persistent-CAP should be defined as a cough occurring for $\geq$2 weeks following surgery [8]. We believe that earlier detection provides greater benefit for patients; the diagnostic duration of persistent-CAP should therefore be shorter than that of chronic cough.

Studies have shown that the incidence of CAP ranged from 24.4 % to 55.0 % [3–5]. This variability could be attributed to inconsistencies in inclusion criteria regarding the duration and severity. Defining severity is indispensable because mild cough may not have a significant impact on the patients.

Based on the aforementioned studies and our experience, we propose a novel definition for persistent-CAP: (1) non-productive cough occurring after pulmonary resection that usually exacerbates when speaking or taking a deep breath but relieves at rest; (2) cough symptoms lasting for $\geq$2 weeks; (3) a visual analog scale (VAS) score for cough of $\geq$60 mm (range: 0–100 mm) [13]; (4) no positive results on chest X-ray (e.g., consolidation, interstitial inflammation); and (5) no postnasal drip syndrome, asthma, pulmonary infection, or ACEI administration.

According to this novel definition, our unpublished multicenter research conducted at Guangdong Provincial People's Hospital and Shenzhen People's Hospital revealed that more than 25.76 % of evaluated patients experienced persistent-CAP, and the mean duration of symptoms was 58 days. We anticipate more research on persistent-CAP to apply this definition in the future.

5. Severity assessment of persistent cough after pulmonary resection

As mentioned above, severity and duration are indispensable for the assessment of persistent-CAP. Regarding severity, there are several validated tools available to assess postoperative cough (Table 1) [14]. For example, the cough VAS is a brief and simple measurement of cough severity and frequency that is widely used in clinical practice. Morice assessed cough severity in participants with chronic cough using the VAS administered within a randomized placebo-controlled study [15]. However, the VAS is not applied to evaluate duration. In addition, the Cough Symptom Score is another subjective tool capturing cough frequency [16].

According to ACCP guidelines for cough diagnosis and treatment, two health-related quality of life questionnaires, the Leicester Cough Questionnaire (LCQ), and the Cough-Specific Quality of Life Questionnaire (CQLQ) are employed extensively to assess cough in patients [20]. The LCQ, a questionnaire [17] that investigates the effects of chronic cough severity regarding physical, psychological, and social aspects, provides a valid, repeatable 19-item self-completed QOL measure (total score spanning 3 to 21), where elevated scores denote an enhanced QOL. Lin et al. administered a Chinese version of the LCQ to assess postoperative cough in 130 patients with NSCLC and suggested this questionnaire to be a reliable, valid instrument [9]. However, the frequency and severity of cough symptoms were not assessed with this questionnaire. Specifically, the CQLQ contains more items that deal with the physical effects of cough [21].

Although these subjective instruments are commonly used and were proved to be valid, an instrument combining subjective and objective measurements is desirable. Objective measurements, including cough frequency monitoring, are increasingly being evaluated as primary outcomes in antitussive medication trials. Additionally, current cough scales are not used exclusively for persistent-CAP. Further work is required to develop persistent-CAP-specific scales that include the evaluation of risk factors, thereby providing fresh insights into persistent-CAP.

6. Risk factors

Cough is a vital defensive reflex, and an imbalance between certain stimuli and responses results in increased coughing [18]. Although the detailed mechanisms of persistent-CAP are not yet understood, based on previous studies, we found persistent-CAP is related to surgical intervention, anesthesia factors, and other factors.

6.1. Surgical intervention

The surgical procedure is the major factor influencing persistent-CAP [3,8]. Invasive surgery inevitably causes physical trauma and architectural distortions, which participate in the pathophysiology of persistent-CAP. However, the exact mechanisms underlying persistent cough caused by surgery remain unclear.

6.1.1. Surgical approaches

Persistent-CAP is associated with specific surgical approaches. In a longitudinal study, Dai et al. enrolled 174 patients to compare patient-reported outcomes between uniportal and multiportal video-assisted thoracoscopic surgery (VATS) for lobectomy [19], determining that uniportal-VATS may produce less coughing ($P = 0.003$) and a more favorable functional condition compared to multiportal-VATS over a six-day postoperative hospitalization. The higher risk of multiportal-VATS may reflect increased number of surgical incisions, resulting in more physiological disruption. Unfortunately, cough symptoms following uniportal-and multiportal-VATS in the late postoperative period have not been determined.

6.1.2. Extent of resection

In a prospective study, Pan et al. investigated predictive factors for cough following uniportal-VATS [5], showing that the extent of resection was an independent factor of persistent-CAP. Subjected to identical circumstances, lobectomy caused greater distortion of structures and function than sublobar resection. In a longitudinal study, sublobectomy produced better cough-associated QOL and faster recovery of postoperative cough compared to lobectomy in patients with NSCLC [22]. The reasons for these differences may be partly explained by the fact that lobectomy produces a greater displacement of the remaining lungs and diaphragm than sublobectomy, thereby affecting airflow dynamics and changing cough reflex sensitivity. In contrast to the earlier findings, Wu et al. demonstrated that, when the same lymph node management method was applied, there was no difference in persistent-CAP severity among patients undergoing wedge resection, segmentectomy, or lobectomy [23]. Another prospective cohort studies have likewise failed to discern

Table 1
Summary of cough assessment tools.

Tools	Items	Cough Characteristics			Impact of Cough on Quality of Life				
		Intensity	Frequency	Duration	Physical	Psychological	Social	Functional	Emotional
VAS [16]	1	+	+	–	–	–	–	–	–
CSS [17]	2	–	+	–	–	–	–	–	–
CQLQ [18]	28	–	–	–	+	+	–	+	+
LCQ [19]	19	–	–	–	+	+	+	–	–

VAS = Visual Analog Scale, CSS = Cough Symptom Score, CQLQ = Cough-Specific Quality of Life Questionnaire, LCQ = Leicester Cough Questionnaire.

any association between the extent of resection and persistent-CAP [24,25].

Pulmonary resection alters the pulmonary structure, leading to an abnormal increase in air flow velocity and shear stress. Gu et al. used CT imaging and computational fluid dynamics to analyze favorable and unfavorable remodeling following left upper pulmonary lobectomy [26]. Unfavorable remodeling factors contributing to postoperative breathlessness, persistent cough, and inflammation encompassed sigmoidal distortion of the left main bronchus, reduction in the angle between the left main bronchus and trachea, and narrowing of the left lower lobe bronchus. On the other hand, bronchial morphological alterations subsequent to right upper lobectomy in lung cancer patients were examined by Lu and colleagues [27]. Their investigation revealed independent associations between postoperative refractory cough and factors such as bronchial kink, stump length, and diameter modifications in the basal bronchus of the right lower lobe. However, these researchers analyzed surgical sites separately. Ueda et al. previously conducted a study in patients undergone upper lobectomy to investigate the effects of postoperative bronchial kinking on pulmonary function using three-dimensional CT-based bronchography [28]. Bronchial kinking after upper lobectomy, which was observed in 41 % of the patients, was associated with reduced postoperative functional lung volume, breathlessness, and persistent cough. Interestingly, two studies showed that right upper surgical site contributed more to the development of CAP than other sites [5,29]. Because the upward displacement of the residual pulmonary lobes and the diaphragm following upper lobectomy, the residual ipsilateral bronchus experiences sigmoidal distortion. (Figs. 1 and 2). These distortions can potentially lead to bronchial angulation, resulting in the constriction or obstruction of airways. The presumption is that structural variations triggering high-velocity airflow mechanically stimulate the rapidly adapting receptors (RARs) in the main airway tract. This stimulation travels via Aδ nerve fibers to activate the cough center in the brain, subsequently inducing the act of coughing.

6.1.3. Lymph node dissection

Previous studies have shown that mediastinal lymph node dissection was an independent risk factor of persistent cough after pneumonectomy [5,8,29]. One possible explanation for these results may be nerve damage. While performing subcarinal lymph node resection, it proves challenging to prevent inadvertent harm to the vagal nerve branches that extend throughout all lung lobes. As portions of the tracheobronchial tract, pulmonary C-fibers are often damaged by severing the vagal nerve, thereby causing cough following lymph node resection. Another mechanism underlying these effects is that a residual cavity is left following lymph node dissection, exposing the RARs located below the carina and around the main bronchus, especially when the superior mediastinal and subcarinal lymph nodes are dissected. Due to cavity formation, cough receptors can be stimulated more easily by chemical stimulation of the postoperative pleural fluid and mechanical pull caused by physical activity. In addition, a randomized controlled trial showed that the intraoperative use of mediastinal adipose tissue to fill the residual cavity following lymph node dissection effectively reduced the incidence of postoperative intractable cough [30]. Nevertheless, the prospective multi-center study conducted by Sun and colleagues did not identify lymph node dissection as an independent risk factor [24].

6.1.4. Postoperative gastroesophageal acid reflux

Several adverse consequences ensue subsequent to pulmonary resection, encompassing reductions in lung volume and diaphragm elevation [31]. These outcomes contribute to a decrease in intrathoracic pressure and constrain diaphragmatic functionality. Such conditions cause postoperative gastroesophageal acid reflux (GER) in patients who underwent pulmonary resection. Pan et al. found

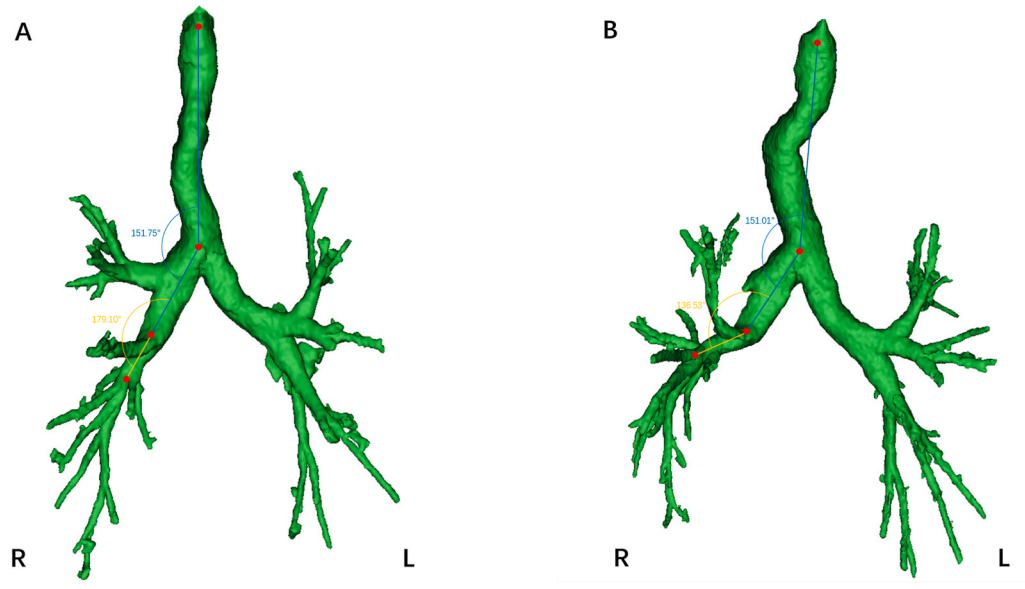

Fig. 1. Three-dimensional image showing structural alterations of tracheobronchial trees of case 1 after right upper pulmonary lobectomy. A. Preoperative global appearance. B. Postoperative global appearance.

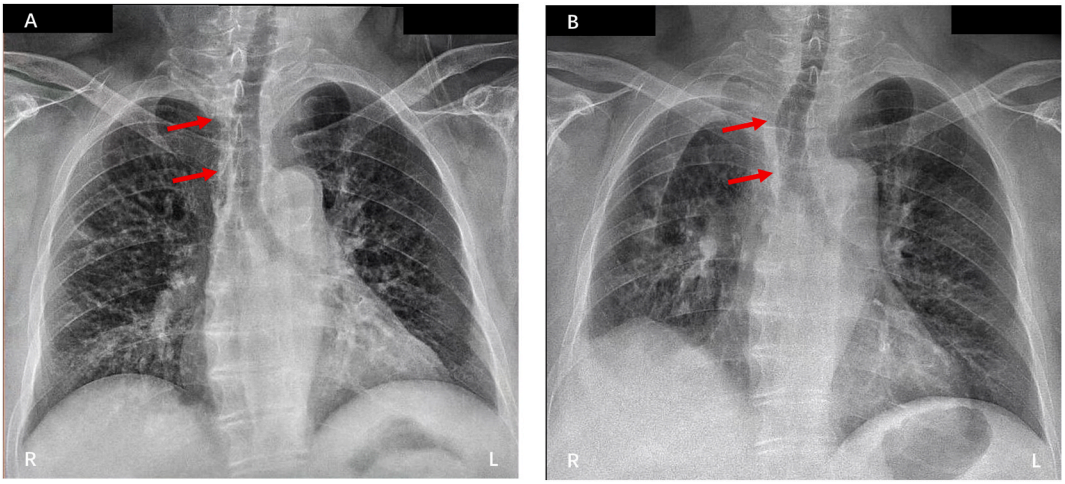

Fig. 2. Chest X-ray showing structural alterations of tracheobronchial trees of case 2 after right upper pulmonary lobectomy. A. Preoperative global appearance. B. Postoperative global appearance.

that postoperative acid reflux was a risk factor for CAP [5], while our prospective multi-center study also revealed the similar results. In an observational study conducted by Sawabata et al., patients were asked about GER symptomology after pulmonary resection with six questions after pulmonary resection [8]; the results emphasize the contribution of GER to cough symptom following pulmonary resection. However, these studies did not verify the contribution of GER to cough symptoms through a definitive examination. Thereupon, Sawabata et al. conducted an observational study in which a 24-h esophageal pH monitor was employed for patients with cough and no cough after lobectomy, revealing a relationship between cough and GER [11].

6.2. Anesthesia-related factors

6.2.1. Intubation-related factors

Anesthesia modalities and medicines are closely related to persistent-CAP. Traditional endobronchial double-lumen general anesthesia is an important procedure in thoracoscopic surgery. However, intubation has been suggested to be associated with a high probability of persistent-CAP. Chen et al. reported that individuals undergoing intubated thoracoscopic lobectomy exhibited higher rates of sore throat (40.0 % vs 6.7 %, P = 0.002) and longer postoperative hospitalizations (7.1 vs 5.9 days, P = 0.078) than non-intubated patients [32]. However, a relationship between cough and intubation was not demonstrated in this comparative study.

In a single-institution study, Chen and colleagues investigated the influence of diverse anesthesia techniques on postoperative cough within a cohort of 1381 patients undergoing lung surgery [10]. Patients were categorized into double-lumen tube (DLT) group and spontaneous respiration group. The incidence of cough in the DLT group (48.9–65.1 % at three months; 20.5–22.8 % at one year) was notably higher compared to that within the spontaneous respiration group (27–36 % at three months; 2.6–7.9 % at one year). The researchers deduced that employing spontaneous respiration anesthesia may lower the probability of coughing, enhance postoperative recuperation, and elevate the overall QOL for patients after surgery. Several factors could explain the high incidence of persistent-CAP in patients undergoing DLT anesthesia. First, DLT intubation induces stress, congestion, and inflammation of the airway mucosa [33] (an important pathological mechanism mediating chronic cough) [34]. Second, inflammatory damage and dryness of the respiratory tract following tracheal intubation further impair airway epithelial cells [35,36]. Cough receptors are exposed and susceptible to external stimuli, leading to hyperresponsiveness [37]. Third, DLT anesthesia with single-lung ventilation alongside lung recruitment potentially induce oxidative stress and exacerbate the consequences of ischemia-reperfusion injury [38]. The duration of anesthesia with intubation has been proven to affect postoperative cough in earlier studies. Lin et al. enrolled 198 patients with NSCLC to identify risk factors for cough after VATS using the LCQ-MC. A prolonged anesthesia duration was determined to be an independent risk factor [3,5]. Similarly, our prospective multi-center study showed that anesthesia duration more than 156 min was a risk factor for persistent CAP.

Extended duration of the DLT residing within the throat and trachea intensifies the extent of compression exerted by the catheter on the tracheal mucosa. Furthermore, when the catheter balloon's pressure surpasses the capillary pressure within the mucosa, it triggers mucosal ischemia, resulting in tissue edema and inflammation. The buildup of acidic compounds and alterations in airway pH levels during inflammation can activate C-fibers, stimulate nerve centers, and initiate airway neuroinflammation [36], consequently elevating the incidence of persistent-CAP occurrence. Difficulties in airways can lead to prolonged intubation times [4]. Airway edema and histamine release also elicit RARs activity, resulting in reflexive cough [37].

6.2.2. Anesthesia medicines

Desflurane and sevoflurane are widely used for maintenance of anesthesia in ambulatory settings. The use of these medicines is

believed to be associated with a high incidence of cough during the emergence period [39,40], whereas the correlation between cough during the long-term postoperative period and desflurane or sevoflurane use is yet to be clarified. Opioids, including fentanyl, remifentanil, and sufentanil find extensive application in the initiation and maintenance of general anesthesia. Opioids may play a role in the inhibition of sympathetic outflow and stimulation of the parasympathetic nervous system. Activation of the vagus nerve has also been suggested to cause cough [41]. Opioid-induced cough has been documented in previous investigations [42,43]; however, it is mostly transient, which is inconsistent with the definition of persistent-CAP.

6.3. Other factors

6.3.1. Preoperative comorbidities

Factors other than those related to surgery and anesthesia may also lead to persistent-CAP. A medical history involving chronic obstructive pulmonary disease (COPD) was a risk factor for chronic cough after surgery [4]. Cough reflex sensitivity appears to be increased in patients with COPD [20], in addition, surgical stimulation and postoperative inflammatory reactions may further aggravate airway hypersensitivity and lead to persistent-CAP.

6.3.2. Female sex

Lin et al. found that female sex is an independent risk factor for persistent-CAP [3]. These observations suggest a gender disparity in cough sensitivity among individuals with chronic cough, similar to outcomes indicated in previous research [44,45]. This phenomenon might be attributed to hormonal effects and heightened visceral sensitivity in women, in conjunction with airway afferent nerves exhibiting hypersensitivity towards the somatosensory cortex [44,46].

7. Prevention

Being among the prevalent complications subsequent to pulmonary resection, persistent-CAP is a major hurdle in the ERAS pathway [47]. Therefore, effective prevention targeting the risk factors of persistent-CAP are of critical importance.

7.1. Surgical prevention

The primary prevention against persistent-CAP is intraoperative prophylaxis. Extensively distributed within the lungs, the vagus nerve gives rise to pulmonary branches that span the respiratory system. Its activation prompts bronchoconstriction, secretion of mucus, and vasodilation of bronchovascularity, ultimately culminating in the onset of coughing [48]. A recent study by Gu et al. showed that the preservation of branches of pulmonary vagal nerve during VATS resulted in a diminished occurrence of CAP compared with conventional surgical treatment (13.89 % vs. 30.43 %, $P = 0.018$) [49]. During thoracic surgery, preventing vagus nerve disconnection or damage can avoid or minimize persistent-CAP.

Interestingly, intraoperative tamping of the residual cavity caused by surgery, such as stoned adipose tissue or gelatin sponge, can greatly reduce the occurrence of persistent-CAP [30]. Through diminishing the provocation of pleural effusion and mitigating the mechanical strain on receptors, the introduction of fatty tissue autografts into residual cavities after lymphadenectomy emerges as a secure and efficient approach to addressing cough subsequent to substantial mediastinal lymphadenectomy and pulmonary resection.

The standard radical surgery of lung cancer entails anatomical lobectomy in conjunction with systematic lymph node dissection [50]. However, lymph node resection is an independent risk factor for cough after pulmonary resection [23]. Chen et al. evaluated different lymph node dissection procedures in VATS for right NSCLC [51] and proposed a novel technique to mediastinal lymph node dissection termed tunnel-type *en bloc* dissection; this method involves functionally dissecting the 2R, 4R, and 7 stations of lymph nodes. Similar to a mining tunnel, this procedure preserves the mediastinal pleura while reducing stimulation of the vagus nerve. The tunnel-group exhibited a lower incidence of postoperative chronic cough than the routine group. Therefore, tunnel-type *en bloc* mediastinal lymph node dissection may play a role in preventing persistent-CAP.

The standardization of the necessity to divide the inferior pulmonary ligament through upper lobectomy remains pending. Kim et al. concluded that the division of the inferior pulmonary ligament did not result in notable variations in lung volume, alterations in bronchial angles, or a decline in forced vital capacity [52]. However, due to the retrospective nature of this study, a comprehensive assessment of cough symptoms was not feasible. Conversely, Moon and colleagues argued that maintaining the integrity of the inferior pulmonary ligament during upper lobectomy could potentially offer advantages in facilitating expansion of the lower lobe with reduced main bronchial movement [53], thereby theoretically mitigating the occurrence of persistent-CAP. Consequently, the advantages of preserving the pulmonary ligament in preventing persistent-CAP remain subject to ongoing debate.

7.2. Anesthesia prevention

With the development of thoracoscopy and the spread of rapid rehabilitation surgery, non-intubation and reserved breathing anesthesia methods in thoracoscopic lung surgery have received increasing attention. The safety and viability of non-intubated thoracoscopic lobectomy have been proven, compared with thoracic surgery under conventional intubated anesthesia [32,54]. An earlier study reported that patients undergoing non-intubated thoracoscopic lobectomy experienced reduced instances of sore throat and shorter postoperative hospital stays than intubated patients [32]. Unfortunately, the relationship between cough and intubation has not been demonstrated.

According to a study by Chen [10], the likelihood of cough within the spontaneous respiratory group was notably diminished compared to the DLT group across all time intervals, and the severity of cough symptoms was more pronounced in the DLT group. Liu et al. recruited 354 patients in a randomized controlled study evaluating the advantages of non-intubated VATS under epidural anesthesia [33]. Non-intubated epidural anesthesia resulted in statistically significantly fewer intubation-associated complications including sore throat, hoarseness, and irritating cough. than DLT anesthesia. Furthermore, the routine omission of muscle relaxants during non-intubated anesthesia facilitates faster recovery of pulmonary function and a decreased occurrence of postoperative respiratory complications. As a result, physicians are able to decrease the occurrence of persistent-CAP by adopting tubeless anesthesia, including combinations of intravenous and intercostal nerve block technique, and intravenous composite epidural anesthesia [33,55].

In situations where tubeless anesthesia technology is contraindicated, other measures can be implemented to decrease persistent-CAP in patients undergoing tracheal intubation. Topical steroids have been used as a treatment for many years. In a study by Chakib et al., the researchers coated an endotracheal tube with betamethasone gel and found a marked decrease in the incidence of cough after tracheal intubation [56]. In addition, inhaled fluticasone was found to decrease the incidence and severity of postoperative cough among patients undergoing general anesthesia [57]. The use of lidocaine to inflate the endotracheal tube cuff or the use of intravenous lidocaine at the end of surgery was also found to decrease the frequency of postoperative cough [58]. Betamethasone gel has been suggested to reduce the incidence and severity of postoperative cough to a greater extent than lidocaine jelly [59]. In a simple approach, preoperative gargling with licorice solution can potentially attenuate postoperative cough after tracheal intubation [60,61]. After the tracheal tip passes the glottis, rotation of the DLT by 180° can decrease postoperative hoarseness and sore throat [62]. However, although this technique facilitates the passage of the DLT and reduces stimulation of the pharynx, larynx, and trachea, it is uncertain whether it can decrease postoperative cough.

8. Treatments

8.1. Medical treatment

Evidence supporting the management of persistent-CAP is limited. To date, no standard therapeutic guidelines have been established for persistent-CAP. This review presents suggestions for medical treatments based on reliable evidence. Methoxyphenamine is recommended as an empirical treatment for addressing chronic cough in patients necessitating a pharmacological intervention; it is also applied to treat postoperative cough clinically [63]. Centrally acting non-addictive drugs, such as dextromethorphan and pentoxyverine, are widely used. This category of antitussive therapy is effective for addressing cough after pulmonary surgery and carries only minor addiction risk [64]. Centrally acting addictive drugs such as codeine and pholcodine are recommended for patients with persistent cough and pain after pulmonary surgery [65]. Levodropropizine, narcodine, and moguisteine are peripherally acting antitussives that may also be effective [66]. Suplatast tosilate is a novel selective Th2 cytokine inhibitor shown to inhibit airway hypersensitivity, a potential mechanism underlying persistent-CAP [67]. Regarding patients reporting acid regurgitation and persistent cough postoperatively, proton pump inhibitors can improve symptom of persistent-CAP [5,8,11].

8.2. Speech and language therapy

Speech and language therapy plays a role in cough management by disrupting the cycle of reciprocating stimulation of cough receptors. This is achieved through enhancing voluntary cognitive regulation of the impulse to cough, decreasing sensitivity of the cough reflex, mitigating irritation in the larynx, and reducing tension in laryngeal muscles [68]. This therapy enables patients to actively control their urge of coughing. These interventions encompass a range of strategies including education, laryngeal hygiene practices, cough suppression techniques, breathing exercises, behavior modification, and psychoeducational counseling [69]. However, the application of speech and language therapy in persistent-CAP is limited. Further research is imperative to elucidate the definitive impact of this therapy on persistent-CAP.

8.3. Traditional Chinese medicine

A comprehensive treatment of persistent-CAP involves multiple strategies. Acupuncture, a fundamental element of traditional Chinese medicine, has emerged as a significant therapeutic modality. A randomized controlled trial has revealed that acupuncture contributes to a reduction in lung-related complications, including CAP, expedite postoperative recovery, and enhance patient prognoses [70]. The underlying mechanisms responsible for these effects encompass dampening inflammatory reactions and diminishing levels of pro-inflammatory factors [70]. The efficacy of acupuncture therapy in addressing chronic cough after lung cancer surgery had been investigated in a retrospective cohort study. Patients receiving acupuncture exhibited notably higher LCQ-MC scores compared to the control group. This outcome suggests that acupuncture has the potential to ameliorate persistent-CAP and its impact on the QOL of affected individuals [4]. There is still a paucity of research on traditional Chinese medicine treatments for persistent-CAP. Given the unique characteristics of traditional Chinese medicine, the understanding of its mechanisms and the clinical application scenarios are still relatively limited. However, the existing studies provide a more diversified perspective for the treatment of persistent-CAP.

9. Comment

As one of the most common complications of pulmonary resection, persistent cough represents a major hurdle on patient QOL and recovery pathway. This review proposes a comprehensive definition for persistent-CAP. We identified risk factors for persistent-CAP including surgical approaches and site, resection extent, lymph node dissection, postoperative gastroesophageal acid reflux, tracheal intubation anesthesia, anesthesia medicines, history of COPD, and sex. Furthermore, improving persistent-CAP requires a combination of comprehensive preoperative assessment, intraoperative prevention targeting risk factors, and postoperative treatment. Prevention of persistent-CAP encompasses two principal approaches: surgical prevention, with meticulous intraoperative handling of nerves, lymph nodes, and pulmonary ligaments; anesthetic prevention, through the utilization of non-intubation anesthesia techniques and the administration of optimal anesthetic agents. A comprehensive treatment of persistent-CAP involves multiple strategies, including medical treatment, speech and language therapy, and traditional Chinese medicine. This review identifies gaps in our knowledge as well as areas for future research.

There were certain limitations in our study. First, we included only full-text articles that were published in English and peer-reviewed. Second, certain risk factors were reported in only a single relevant study, precluding the ability to conduct a meta-analysis to derive a reliable and generalizable result. We anticipate that future research in this domain will expand the evidence base, thereby enhancing the credibility of these findings. Third, the definition of persistent-CAP lacks uniformity across various studies, with inconsistencies in its duration and the severity not provided explicitly. In certain studies, definitions are absent, with the definition of persistent-CAP being contingent upon either physician determination or patient self-reporting. This variability accentuates the necessity for our research to establish a unified comprehensive definition.

In conclusion, a definition for persistent-CAP was proposed in this review. Risk factors for persistent-CAP were identified as surgical intervention, anesthesia-related factors and other factors. And prevention targeting risk factors and multimodal treatments are summarized. There is a pressing need for prospective, multicenter, randomized controlled studies to comprehensively unravel the underlying mechanisms of persistent-CAP, and to track dynamic changes of persistent-CAP symptom and outcomes of intervention.

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Ethics statement

Review and/or approval by an ethics committee was not needed for this study because the manuscript submitted was a review. Informed consent was not required for this study because no participants were enrolled or involved in the research process.

Data availability

Sharing research data helps other researchers evaluate your findings, build on your work and to increase trust in your article. We encourage all our authors to make as much of their data publicly available as reasonably possible. Please note that your response to the following questions regarding the public data availability and the reasons for potentially not making data available will be available alongside your article upon publication.

Has data associated with your study been deposited into a publicly available repository?

Response:No. Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Xuefeng Sun: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Zihua Lan:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Qiuling Shi:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Funding acquisition, Formal analysis, Data curation. **Hansheng Wu:** . **Guojie Lu:** . **Yuan Qiu:** Writing – review & editing, Writing – original draft, Investigation. **Yong Tang:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition. **Guibin Qiao:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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.

Appendix A. Supplementary data

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