Original Article

A postoperative comparison of high-flow nasal cannula therapy and conventional oxygen therapy for esophageal cancer patients

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Background: Hypoxaemia in post-surgical patients of esophageal cancer (EC) is common in thoracic departments. However, few studies have investigated the role of high-flow nasal cannula (HFNC) compared with conventional oxygen therapy (COT).

Methods: A retrospective study was implemented to enroll hypoxemic patients after esophagectomy who were treated by HFNC or COT immediately after extubation between January 2019 and December 2019. We compared the effect of HFNC or COT in patients regarding the vital signs and arterial blood gases, the incidence of anastomotic leakage, postoperative pulmonary complications (PPCs), sore throat/nose, and reintubation, length of stay, and sputum production. We also 3D reconstructed the postoperative chest CT, and compared the amount of lung volume loss caused by PPCs (pneumothorax, atelectasis, pulmonary consolidation and pleural effusion) between the two groups.

Results: Compared to patients in COT group, sore throat/nose in HFNC group was lower, the sputum production was higher, and the total hospital stay was shorter. Compared to COT, HFNC treatment decreased systolic blood pressure (SBP) at day 1, diastolic blood pressure (DBP) at day 1–4, and heart rate (HR) at day 2–4, increased arterial partial pressure of oxygen (PaO_2) at day 1–4, and arterial oxygen saturation (SaO_2%) at day 1–2. In addition, the rate of PPCs and anastomotic leakage in HFNC group were lower than those in COT group. Compared to COT, HFNC treatment significantly decreased the amount of lung volume loss caused by PPCs.

Conclusions: HFNC can improve the hypoxemia of patients after esophagectomy, increase the flow of sputum, reduce the incidence of PPC and anastomotic leakage.

Keywords: High-flow nasal cannula (HFNC); esophageal cancer (EC); post-operation; hypoxaemia

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Introduction

Esophageal cancer (EC), with its high risk of metastases and recurrence, is the 4th highest deadliest cancer among all cancer types and one of the most prevalent in China (1-3). One of the effective treatment options for EC patients is radical esophagectomy, though it is known to be associated with a high mortality rate (4), which might be due to several factors. EC patients usually suffer from compromised digestive and immune system; they may also deal with tobacco and alcohol addiction. On top of these conditions, they also have to recover from the severe injuries they suffered during the operation, such as long operation time and vast area of trauma that often involves neck, chest, and abdomen. Moreover, patients are often known to develop multiple postoperative pulmonary complications (PPCs) and anastomotic leakages (5). During the past few years, multiple large-sample prospective clinical studies reported that high-flow nasal cannula (HFNC) could reduce the incidence of PPCs while others disagreed, and Pennisi reported (6) similar incidence of PPCs in their post-lobectomy patients. In addition, several institutions have also applied HFNC to cardiac surgery patients and proven that HFNC can improve the comfort of patients after cardiac surgery and reduce the need to upgrade respiratory support (7). However, few studies have analyzed the effectiveness of postoperatively HFNC to the treatment of hypoxemia for EC patients. In the present study, we aimed to determine whether postoperative application of HFNC is superior to conventional oxygen therapy (COT) for EC patients.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1539).

Methods

Patients selection

We had compared HFNC with COT in parallel for 1 year until it totally replaced COT for hypoxemic patients in 2019 (HFNC was introduced into our Department in August 2019. Before that, COT was used in all patients after esophagectomy, and HFNC was used after that). The clinical data of those patients weaned from mechanical ventilation were collected from January 1, 2019 to December 31, 2019 after esophagectomy in the Thoracic Surgery Unit of our hospital.

Patients with postoperative hypoxemia were enrolled in the study. Postoperative hypoxemia was defined as 100 mmHg ≤ arterial partial pressure of oxygen/fraction of inspiration oxygen (PaO_2/FiO_2) <300 mmHg after weaning from mechanical ventilation, as used previously. The hypoxemia was also diagnosed as arterial oxygen saturation (SaO_2) <92%, respiratory rate (RR) >30 breath/min, without respiratory failure caused by other complications such as bleeding and heart failure. Patients were excluded from the study if they had (I) clinical history of underlying chronic obstructive pulmonary disease, (II) cardiogenic pulmonary edema, (III) tracheostomy, (IV) delirium, nausea and vomiting, (V) impaired consciousness or disorientation, (VI) hemodynamic instability, (VII) sudden cardiac arrest, (VIII) moderate to severe respiratory acidosis hypercapnia (pH <7.30) combined with multiple organ dysfunctions. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of Southwest Hospital (IRB number: KY201846) and individual consent for this retrospective analysis was waived.

Postoperative treatments

Patients in the thoracic surgery ICU were placed on routine monitoring. In our practice, all hypoxemic patients eligible for inclusion were immediately treated after extubation with either COT or HFNC oxygen therapy. Patients in COT group received oxygen via either nasal prongs or facemasks with oxygen flow titrated by the bedside clinician to maintain a peripheral oxygen saturation ($SpO_2\% \geq 95\%$). For patients wearing a nasal cannula or a simple face mask, each additional liter/min of oxygen added about 4 percentage points for the first 3 liters and only 3 percentage points for every liter thereafter to the desired $FiO_2\%$. Patients in the HFNC (Optiflow^{TM} Nasal High Flow; Fisher & Paykel Healthcare, New Zealand) group received oxygen at an intial flow rate of 30 to 40 L/min and $FiO_2\%$ titrated (from 21% to 100%) by the treating clinician to maintain $SpO_2\%$ of ≥95%. The gas temperature was set to 32–37 ℃ with a humidifier. Reintubation was determined by the treating physician based on the general intubation criteria, including increased RR, acute respiratory failure as well as patient intolerance.

Data collection

Patients' information including age, gender, body mass index (BMI), smoking index, pre-surgery forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC),

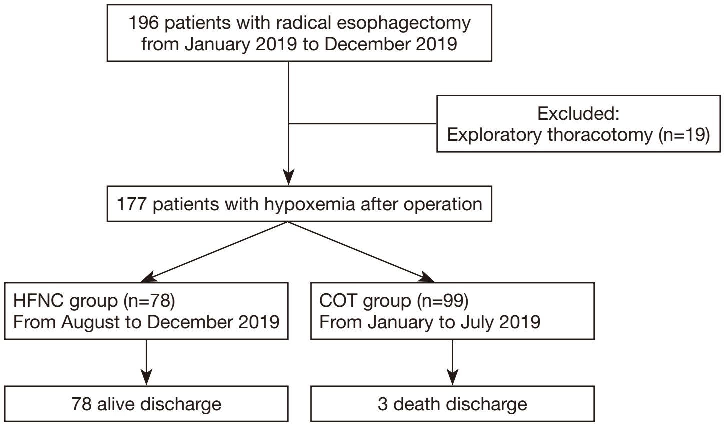

Figure 1 Patient flow chart. HFNC, high-flow nasal cannula; COT, conventional oxygen therapy.

operation time, tumor location, Hb, RR, PaO_2 and thoracoscopic results were obtained from medical record review. The clinical outcomes after oxygen therapy were recorded and used as the primary outcomes to compare the differences between the two groups of patients. In detail, vital signs, arterial blood gases variables in 4 days (if acquired), anastomotic leakage or PPCs (PPCs were defined as atelectasis, suspected pulmonary infection, pleural effusion, and pneumothorax) from the first 10 days of oxygen therapy, sputum production for the first 3 days of oxygen therapy, in-hospital mortality rate, ICU length of stay, length of hospital stay, and events of sore throat/nose and reintubation were recorded. There was no data missing.

Image reconstruction and volume calculation

On the 5th day after operation, we reexamined the two groups of patients with chest CT. With Amira software, the normal lung, pneumothorax, pleural effusion, atelectasis and lung consolidation, and pleural effusion were segmented and 3D reconstructed, and then the 3D model was smoothed and simplified. We measured the lung volume loss which was caused by pneumothorax, atelectasis and pulmonary consolidation, and pleural effusion, and compared the lung volume loss between the two groups.

Statistical analysis

All statistical analyses were performed using SPSS 22.0. Continuous variables were expressed as mean ± standard deviation (SD) or median [interquartile range (IQR)], and categorical variables were presented as n (%). The differences of laboratory findings between groups were compared using *t*-test, Mann-Whitney U test, χ^2 test, or Fisher's exact test as appropriate. Kaplan-Meier curves were also constructed to assess the probability of remaining patients who were free from PPCs after discontinuation of the allocated treatment. And $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

Of the total 196 patients admitted, 19 patients who underwent exploratory thoracotomy were excluded. The remaining 177 patients who underwent radical resection of esophageal carcinoma were enrolled. Among these 177 patients, 78 patients accepted HFNC therapy from August to December 2019, and 99 patients accepted COT from January to July 2019. Among these 99 patients, 3 patients died during the hospital stay. There was no significant difference between the two groups in factors such as intraoperative anesthesia, operation method and operator (*Figure 1*).

Although patients in HFNC group were older and had higher BMI, smoking index and RR than those in COT group, these differences were not statistically significant. Moreover, there were also no significant difference between the two groups of patients in gender, tumor location, preoperative FEV_1/FVC, Hb, PaO_2, operation time and thoracoscopic outcomes ($P<0.05$). These data indicate no significant differences between the two groups in baseline characteristics (*Table 1*).

Table 1 Baseline patient demographic and clinical characteristics of the HFNC and COT groups

Factors	COT (n=99)	HFNC (n=78)	P
Age (y)	60.53±9.39	62.01±7.21	0.812
Gender (male, %)	75 (79.79)	67 (87.01)	0.566
BMI (kg/m^2)	21.74±2.84	23.66±2.44	0.566
Smoking index	483.11±416.98	521.23±543.80	0.103
FEV_1/FVC	81.85±8.61	76.65±10.49	0.585
The operation time (hr)	3.85±1.22	3.67±0.91	0.605
Tumor location			0.516
Upper	39	35	
Middle	24	21	
Lower	36	22	
Hb (g/L)	125.16±18.55	119.33±13.86	0.518
RR (bpm)	15.61±3.14	16.32±2.97	0.683
PaO_2/21%	312.45±12.64	308.26±16.22	0.471
thoracoscope	59 (59.60)	54 (69.20)	0.185

Data are expressed as number (%), mean ± SD, or median (IQR), depending on variable distribution. HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; RR, respiratory rate; PaO_2, arterial partial pressure of oxygen; SD, standard deviation; IQR, interquartile range.

Comparison of the outcome events between the HFNC and COT groups

The total hospital stay was 18.13±3.2 days in the COT group and 14.47±2.6 days in the HFNC group (P=0.041). The proportion of sore throat/nose was 5.13% (4/78) in the HFNC group and 16.2% (16/99) in the COT group (P=0.030). Sputum drainage in the first 3 days was 68.38±9.41 mL in the HFNC group and 56.12±6.93 mL in the COT group (P=0.032). Three patients (3.0%) in the COT group developed severe pulmonary interstitial damage and died of fatal hypoxemia after endotracheal intubation and ventilator treatment, while no patient (0.0%) in the HFNC group died. There was no significant difference in in-hospital mortality rate between the two groups (P=0.256). The reintubation rate was 8.1% (8/99) in the COT group and 3.8% (3/78) in the HFNC group during the treatment (P=0.351). The ICU length of stay was 2.51±0.87 days in the COT group and 2.44±0.68 days in the HFNC group (P=0.570) (*Table 2*).

Comparison of patients' vital signs and arterial blood gases at different time points between HFNC group and COT group

There was no significant difference between the two groups in terms of vital signs and arterial blood gases at the initiation of oxygen treatment. Compared to COT, HFNC treatment significantly decreased systolic blood pressure (SBP) at day 1 (P<0.01), diastolic blood pressure (DBP) at day 1, 2, 3, and 4 (P<0.01), and heart rate (HR) at day 2, 3, and 4, increased PaO_2 at day 1, 2, 3 and 4, and SaO_2% at day 1 and 2, while had no significantly different effects on temperature, RR, FiO_2%, $PaCO_2$ and pH (P>0.05 for all) (*Figure 2*).

PPCs and anastomotic leakage

Kaplan-Meier plots of patients without anastomotic leakage and PPCs from initiation to day 10 after surgery indicated statistically significant between-group difference in the

Table 2 Comparison of the outcome event between the HFNC and COT groups

Factors	COT (n=99)	HFNC (n=78)	P
Sore throat/nose	16 (16.20)	4 (5.13)	0.030
Sputum drainage (mL, in 3 days)	56.12±6.93	68.38±9.41	0.032
Reintubation	8 (8.10)	3 (3.80)	0.351
In-hospital mortality rate	3 (3.00)	0 (0.00)	0.256
ICU length of stay (days)	2.51±0.87	2.44±0.68	0.570
Length of stay (days)	18.13±3.20	14.47±2.60	0.041

Data are expressed as number (%), mean ± SD, depending on variable distribution. HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; SD, standard deviation.

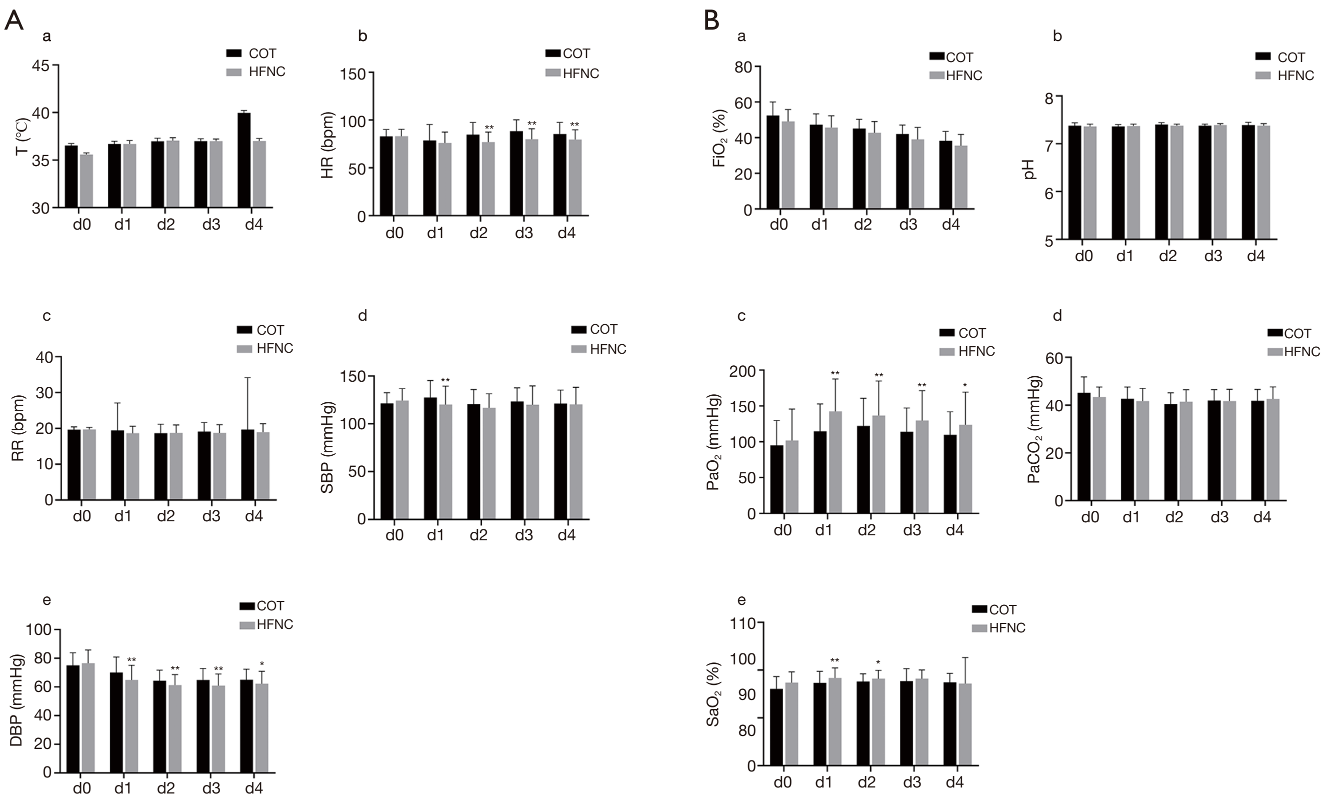

Figure 2 Comparison of variables between HFNC group and COT group in different time points. (A) Vital signs. (a) Auxillary temperature (℃); (b) heart rate (HR); (c) respiratory rate (RR); (d) systolic blood pressure (SBP); (e) diastolic blood pressure (DBP). (B) Arterial blood gases. (a) Fraction of inspiration oxygen (FiO_2%); (b) pH; (c) arterial partial pressure of oxygen (PaO_2); (d) arterial partial pressure of carbon dioxide ($PaCO_2$); (e) arterial oxygen saturation (SaO_2%). *, P<0.05; **, P<0.01. HFNC, high-flow nasal cannula; COT, conventional oxygen therapy.

proportion of patients who remained free of any pulmonary complication during the 10-day postoperative follow-up. The PPCs occurred in 25 out of 99 (25.3%, 95% CI: 8.193–9.151%) patients in the COT group, while only occurred in 4 out of 78 (5.1%, 95% CI: 9.366–9.986%) patients in the HFNC group (P<0.01, log-rank test). The anastomotic fistula occurred in 12 out of 99 (12.1%, 95% CI: 9.006–9.722%) patients in the COT group, while only

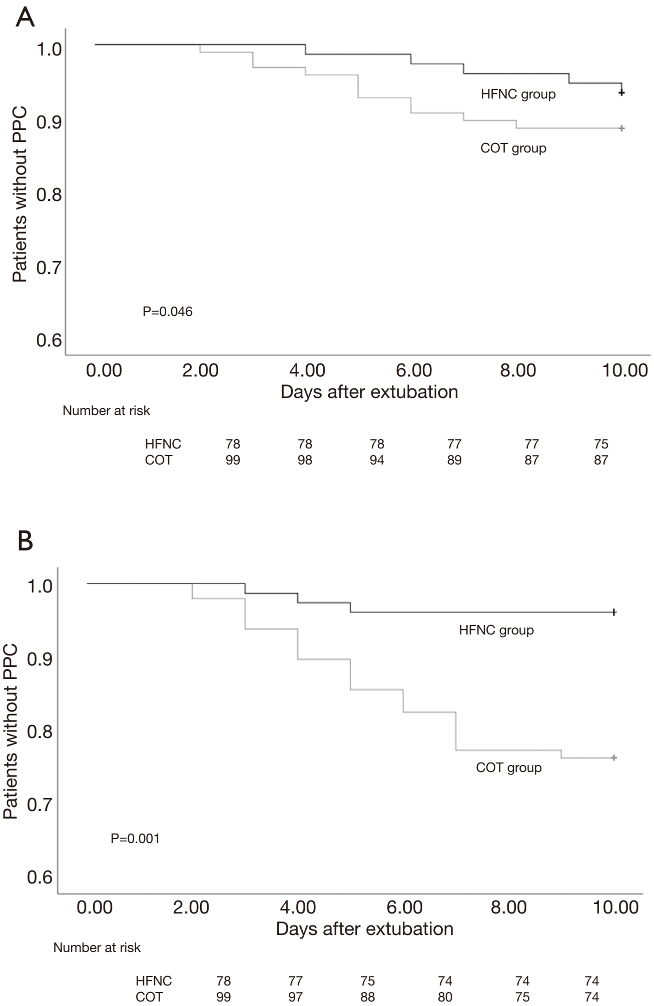

Figure 3 Kaplan-Meier plots of patients without anastomotic fistula or PPCs from post-operation to day 10. (A) Anastomotic fistula; (B) PPCs. HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; PPC, postoperative pulmonary complication.

occurred in 3 out of 78 (3.8%, 95% CI: 9.810–10.062%) patients in the HFNC group (P<0.05, log-rank test) (*Figure 3*).

Image reconstruction and volume calculation

Compared to COT, HFNC treatment significantly decreased the amount of lung volume loss caused by pneumothorax, atelectasis and pulmonary consolidation (*Figure 4*, *Table 3*).

Discussion

Although perioperative management of EC patients has gradually improved, the morbidity and mortality rates after esophagectomy still remained the highest among all solid tumor surgeries. Takeuchi *et al.* (8) reported that out of all 5,354 EC patients who underwent esophagectomy in 713 institutions in Japan, 15.4% developed pneumonia, 13.3% suffered from anastomotic leakage, the 30-day mortality rate was 1.2% (4.3% in United Kingdom, 3.0% in United States) and the operative mortality rate was 3.4%. The respiratory complications are the most common cause of death with the incidence ranging from 19.3% to 44.4% (9). Several studies have shown that the mortality rate after esophagectomy was ranged from 3.8% to 5.8%, and among these patients, 50–56% died from respiratory complications (10,11); the incidence of respiratory complications was ranged from 22.9% to 38.9%; and that of anastomotic leaks was 13% to 35% (12-15). These results suggest that post-esophagectomy treatment is not only a prevention of postoperative complications but also an appropriate management crucial to minimize mortality.

Throat or nasal pain seems correlated with high morbidity in COT (12.96%) due to lack of proper humidity. COT, which includes nasal catheter or mask oxygen absorption, though is lighter and more comfortable than HFNC, could neither accurately deliver fine-tuned oxygen concentration nor heated and humidified gas (16), therefore only rendering limited auxiliary effect on patient's lung. Compared to HFNC therapy, COT caused a higher degree of throat or nasal pain (12.96%) due to its inability to deliver oxygen at a suitable level. In contrast, HFNC provides precise fractional oxygen delivery, a mild-level of positive airway pressure, washout of nasopharyngeal dead space, and a reduced airway resistance (17) and has advantages over other non-invasive ventilation therapy in easier use and better comfortability (18). A randomized controlled trial (RCT) has shown that application of HFNC therapy in adult patients was associated with a lower reintubation rate compared with COT (19). According to the consensus of domestic experts in 2019 (20), HFNC should be applied to patients with mild to moderate hypoxemia (100 mmHg $\leq$ PaO_2/FiO_2 <300 mmHg), no emergency tracheal intubation, and relatively stable vital signs. Therefore, we included patients who underwent radical esophagectomy and had PaO_2/FiO_2 <300 mmHg after offline extubation. In the study of Roca *et al.* (21), HFNC had better comfortability,

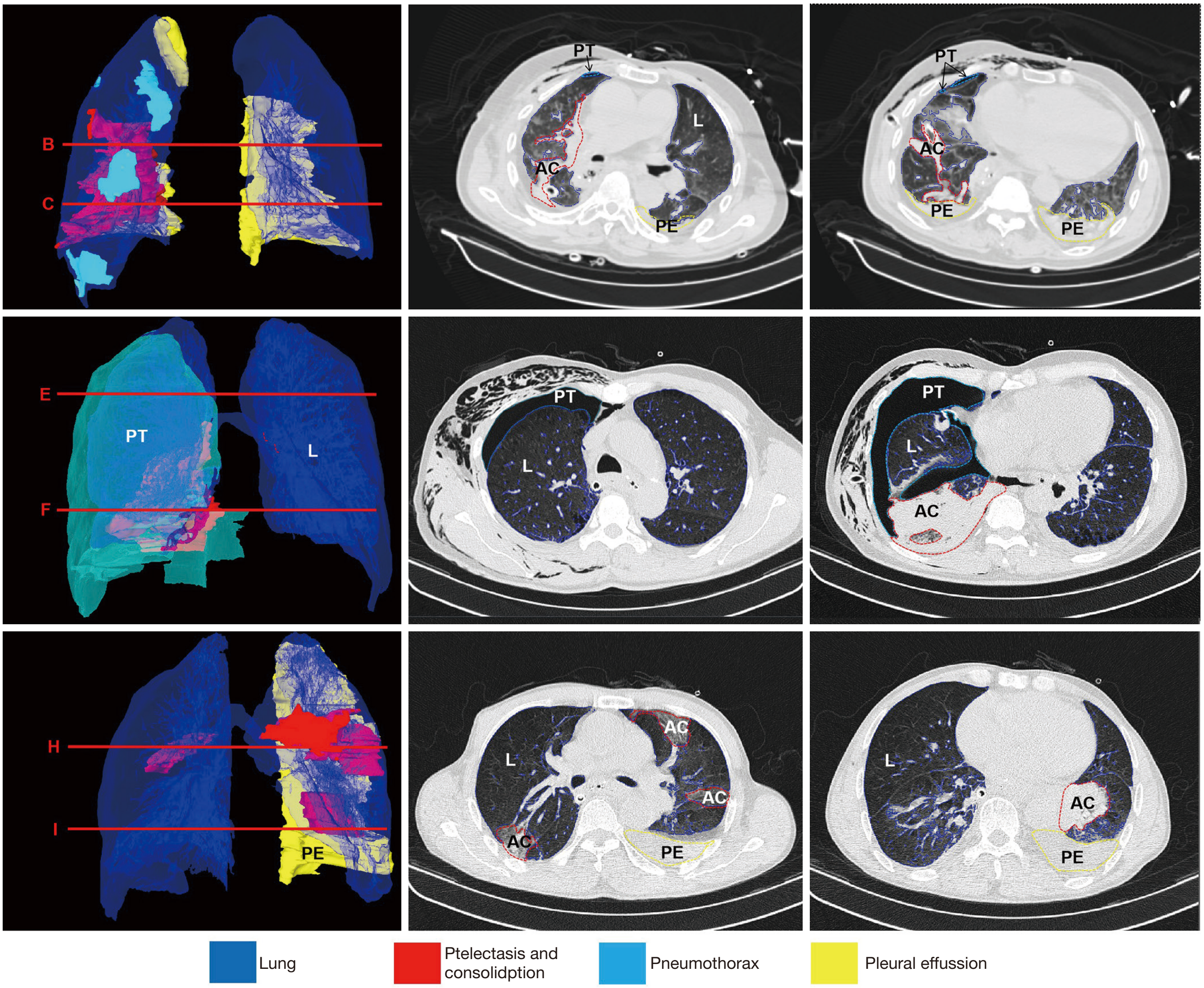

Figure 4 3D reconstruct the normal lung (L), pneumothorax (PT), pleural effusion (PE), atelectasis (AC) and lung consolidation, and pleural effusion.

Table 3 Comparison of the amount of lung volume loss between the HFNC and COT groups

Causes of lung volume loss	COT (n=99)	HFNC (n=78)	P
Pneumothorax (mL)	353.45 (151.65–607.39)	20.78 (6.30–41.35)	<0.001
Atelectasis and pulmonary consolidation (mL)	82.67 (131.25–235.87)	63.20 (20.15–115.63)	<0.001
Pleural effusion (mL)	417.50 (302.38–611.55)	553.76 (251.37–907.63)	0.088

Data are expressed as median (IQR). HFNC, high-flow nasal cannula; COT, conventional oxygen therapy; IQR, interquartile range.

significantly reduced breathing rate and higher oxygenation without significant differences in arterial blood CO_2. Our results also showed that compared with patients in the COT group, patients in the HFNC group had significantly higher oxygenation, significantly lower hospital stay and better comfortability as indicated by lower incidence of nose pain and sore throat. All of these suggest that HFNC improves hypoxia and shortens the length of hospital stay. Sztrymf *et al.* (22) reported that HFNC could significantly reduce respiration rate and chest-abdominal asynchrony, and significantly improve SaO_2%. A retrospective study (23) reports on 75 patients with acute respiratory failure showed that HFNC treatment significantly improved a number of respiratory parameters within 24 h including PaO_2, SaO_2%, RR and HR. A prospective study (24) evaluated the short-term physiological effects of HFNC by measuring parameters such as inspiratory muscle strength, gas exchange, dyspnea score, and comfort level and found that compared to COT, HFNC treatment significantly improved inspiratory power and oxygenation. In this study, the average RR of HFNC group was lower than that of COT group, but there was no significant difference. It may be due to the different disease types (after EC surgery), other factors affecting respiration (such as pain, thoracotomy, etc.), or the insufficient sample size. Compared to COT, HFNC treatment significantly decreased BP and HR, increased PaO_2 and SaO_2%. After EC surgery, BP is often higher than that before operation. The main causes are hypoxia and pain (active expectoration aggravates pain). HFNC can relieve hypoxia, humidify airway, and make sputum easier to be eliminated, thus reducing the pain caused by cough, which may be the reason for lowering BP.

In adults, PPCs are associated with both high mortality and extended ICU stays (25). PPCs are the development of at least one of the following symptoms within 7–30 postoperative days: atelectasis, respiratory failure, pleural effusion, pneumothorax, bronchospasm, respiratory infection, aspiration pneumonitis, and acute respiratory distress syndrome. The main reasons for the occurrence of PPCs are as follows. First, studies have shown that patients undergoing esophagectomy after preoperative chemoradiotherapy were afflicted with more severe respiratory complications and higher operative mortality rate than patients undergoing esophagectomy alone (26). Second, the cause of respiratory complications is multifactorial, such as postoperative minor aspirations, increased fluid load, multiple red cell transfusions, smoking, and genetic susceptibility. In addition, prolonged use of single lung ventilation during esophagectomy may also cause lung injury (27). Patients with squamous cell carcinoma also exhibited a higher incidence of pneumonia and respiratory insufficiency, altogether resulting in twice the overall rate of incidence than that of patients with adenocarcinoma (28). At last, pulmonary function tests may aid in the identification of high-risk patients beyond typical risk factors. In this regard, many studies have incorporated FEV_1 as a predictor for postoperative complications after esophagectomy. In this study, no significant differences in preoperative FEV_1 were found between the patients in HFNC and COT groups, inferring that the difference in PPCs between the two groups was not related to preoperative FEV_1. Several possible reasons might explain why the within 10 days post-operation, patients suffering from hypoxemia after extubation in COT group suffered more complications than in HFNC group. First, HFNC promotes the removal of bronchial secretions by heating and humidifying oxygen so that it reaches the physiologically required temperature and humidity, which in turn is conducive to the recovery of the ciliary system and the active discharge of sputum (29). This is also validated by our findings that the sputum drainage volume of patients in the HFNC group was significant higher than that in the COT group ($P<0.05$). All patients in this study suffered from squamous cell carcinoma, inferring that they are inherently more prone to develop PPCs. Though in this case, the chances should be equal between the two groups. Research has shown that for every 10 L/min increase in HFNC flow rate, patients' pharyngeal positive end-expiratory pressure (PEEP) increases by 0.5–1 cmH_2O and when the flow rate is increased to 60 L/min, the PEEP of the closed oropharyngeal cavities reaches 4–4.7 cmH_2O (30), thereby promoting oxygenation and lung recruitment and improving minute atelectasis. Predictors of anastomotic fistula are advanced age, preoperative chemoradiotherapy, poor physical status, low preoperative serum albumin level, pre-existing diabetes, high pathological stage and low pulmonary function. However, not one study has considered whether the difference in postoperative oxygen therapy was related to anastomotic leakage. Therefore, it is crucial to, after excluding preoperative risk factors, conduct careful and multidisciplinary assessment when administering postoperative oxygen therapy to EC patients. With regard to the pre-operative conditions of patients in the two groups, no significant difference was observed. However, patients in the HFNC group exhibited significantly lower incidence of anastomotic leakage. Factors such as smoking, anastomotic blood supply, perioperative nutritional status, preoperative chemoradiotherapy, hypoxia and pulmonary infection can lead to anastomotic leak after esophagectomy (31-33). In our study, HFNC can significantly improve blood oxygen after esophagectomy and reduce the incidence of pulmonary infection, which may be the reason for the decreased incidence of anastomotic leaks in the HFNC group.

Conclusions

Compared to lung cancer surgery, EC surgery takes longer time and is more invasive. Thus, it often leads to more postoperative complications including hypoxemia (34). The sequential treatment of mild to moderate postoperative hypoxemia with HFNC oxygen therapy effectively improves patients' oxygenation, reduces the incidence of clinical PPC and anastomotic leakage, shortens the length of hospital stay, and promotes patients' recovery and discharge. A large prospective randomized trial would be required to determine whether the modalities of post-extubation oxygen therapy influence weaning success or failure.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-1539

Data Sharing Statement: Available at http://dx.doi.org/10.21037/apm-20-1539

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1539). The authors have no conflicts of interest to declare.

Ethical Statement: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of Southwest Hospital (IRB number: KY201846) and individual consent for this retrospective analysis was waived. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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